



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 8

A. R. Katritzky &
A. J. Boulton

Advances in
Heterocyclic
Chemistry

Volume 8

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Advances in
**HETEROCYCLIC
CHEMISTRY**

Edited by

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Preface

The eighth volume of this serial publication comprises eight contributions from international authors. Four of these deal with well-defined groups of compounds: thiopyrones (R. Zahradník, R. Mayer, and W. Broy), phenoxazines and phenothiazines (M. Ionescu and H. Mantsch), diazepines (F. D. Popp and A. Catala Noble), and benzisoxazoles (anthranils and indoxazenes) (K.-H. Wünsch and A. J. Boulton). J. M. Tedder has surveyed the field of the heteroaromatic diazo compounds which are derived from a variety of heterocyclic ring systems, and M. Schulz and K. Kirschke discuss heterocyclic peroxides. The remaining two chapters survey well-known reactions: the Hilbert-Johnson reaction is covered by J. Pliml and M. Prystaš, and heterocyclic Claisen rearrangements by B. S. Thyagarajan.

We are grateful to the publishers and the authors for their cooperation, which has enabled this volume to be produced more quickly than some of the earlier volumes in this serial publication. We hope to improve this schedule still further in future volumes.

A. R. KATRITZKY
A. J. BOULTON

Norwich, England
December, 1966

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Heterocyclic Diazo Compounds

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I. Introduction

Stable five-membered heterocyclic diazo compounds form an interesting group of compounds. The first example, 3-diazoindazole, was reported by Bamberger in 1899.¹ To reinterpret Bamberger's suggestion for its structure in modern terms is difficult since the structure proposed for indazole itself would be unacceptable. However Bamberger regarded the diazoindazole as an anhydride of the diazonium hydroxide and he suggested it contained a four-membered ring (which he called a triazolen ring). We can therefore depict his structure as in 1.



(1)

"Indazoletriazolen," Bamberger, 1899

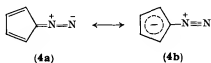
¹ E. Bamberger, *Ber. Deut. Chem. Ges.* **32**, 1773 (1899).

In their first paper on diazoindoles some 5 years later Angeli and D'Angelo again regard the diazo compound as the anhydride of the diazonium hydroxide.² They offered two structures (2 and 3) one of which is very close to today's picture.



Structures for diazoindole, Angeli and D'Angelo, 1904

It is interesting that Taylor and Baker in their brilliant rewriting of Sidgwick's "Organic Chemistry of Nitrogen" should have written of 3-diazodi- and triphenylpyrroles: "the composition of these so-called diazopyrroles resembles that of the aliphatic diazo compounds but their structure is not fully known."³ The real interpretation of the structure and stability of heterocyclic diazo compounds was not forthcoming until 1959. In 1953 Doering and De Puy reported the synthesis of diazocyclopentadiene (4), apparently unaware that heterocyclic analogs had been known 50 years before.⁴ Formula 4b is supposed to represent a combination of the four possible canonical



forms with a negative charge on unsubstituted carbon atoms. The cyclopentadienyl ring then contains six π electrons necessary to make a closed aromatic shell. In fact, the infrared spectrum of diazocyclopentadiene, and of most heterocyclic diazo compounds, shows absorption at 2100 cm^{-1} characteristic of aliphatic diazo compounds (cf. 2200 cm^{-1} for aromatic and heterocyclic diazonium salts). Nevertheless, the exceptional stability of diazocyclopentadiene and the fact that it will undergo electrophilic substitution suggest that the

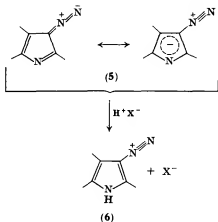
² A. Angeli and A. D'Angelo, *Atti Reale Accad. Lincei* **13**, 258 (1904)

³ T. W. J. Taylor and W. Baker, "The Organic Chemistry of Nitrogen," p. 480. Oxford Univ. Press, London and New York, 1937.

⁴ W. von E. Doering and C. H. De Puy, *J. Am. Chem. Soc.* **75**, 5955 (1953).

canonical forms represented by formula **4b** do contribute to the over-all structure of the molecules.

The heterocyclic diazo compounds such as diazopyrroles bear the same relation to diazocyclopentadiene that pyridine does to benzene. Just as pyridine is a base and forms a pyridinium ion, in acid solution, so diazopyrroles (**5**) form pyrrole diazonium salts (**6**).



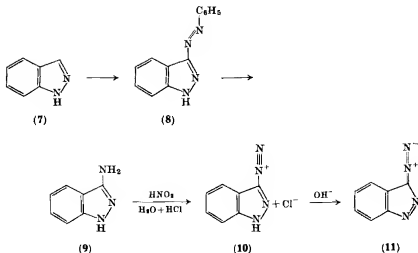
We shall first discuss the preparation of heterocyclic diazo compounds as a class and shall then consider separately the individual characteristics of the various types, e.g., diazopyrroles, diazopyrazoles, etc.

II. Methods of Preparation

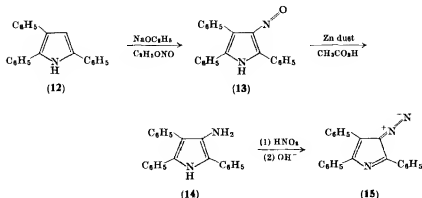
3-Diazoindazole (**11**) was first prepared by the diazotization of 3-aminoindazole (**9**) followed by the treatment of the resulting diazonium salt (**10**) with base.^{1,5} This remains the most important method of synthesis for the whole class of heterocyclic diazo compounds. (See p. 4.)

Pyrrole and indole diazonium salts are acidic and lose a proton even in dilute acid to yield the diazo compound. Pyrazole diazonium salts, on the other hand, are only feebly acidic and the diazo compound is liberated only in quite strong alkali. In many cases the difficulty in obtaining the heterocyclic diazo compound has mainly centered round the preparation of the preceding amino compound. Nitration

⁵ E. Bamberger, *Ann. Chem.* **305**, 289 (1899).



of the heterocyclic nucleus is rarely a satisfactory reaction and for diazopyrroles and indoles nitrosation and reduction of the resulting nitroso compound is a suitable alternative.⁶

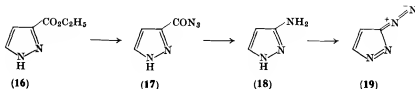


Another route extensively used in the pyrazole series goes via a Curtius rearrangement (16 \rightarrow 19).⁷

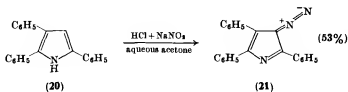
One of the factors which stimulated recent interest in heterocyclic diazo compounds was the application of the technique of direct

⁶ F. Angelico, *Atti Reale Accad. Lincei* **14**, 167 (1905).

⁷ H. Reimlinger, A. v. Overstraeten, and H. G. Viche, *Chem. Ber.* **94**, 1036 (1961).



introduction of the diazonium group. It has been shown that a wide variety of aromatic nuclei can be converted into diazonium salts in one experimental step. Phenol ethers and polyalkylbenzenes require nitrosyl sulfuric acid (either crystalline or prepared *in situ* from sodium nitrite and concentrated sulfuric acid),⁸ deactivated nuclei such as nitro compounds require in addition mercuric ions as catalysts,⁹ but phenols¹⁰ and tertiary aromatic amines¹¹ are converted into diazonium salts in good yield by treatment with excess of nitrous acid. It is customary to emphasize to students the similarity in chemical reactions of phenols and pyrroles. 2,3,5-Triphenylpyrrole (**20**) was therefore treated with an acetone solution of nitrous acid and the corresponding diazo compound (**21**) was obtained¹² (initially the yield was poor but in subsequent work reasonable yields were obtained).¹³



The analogy between phenols and pyrroles is particularly apt in this case because the equilibrium between a phenol diazonium salt (**22**) and a diazooxide (**23**) is exactly analogous to that between a pyrrole diazonium salt (**24**) and a diazopyrrole (**25**). (See p. 6.)

At first it was believed that the reaction could not be applied to pyrroles in which the 2-position was vacant,¹² but subsequent work

⁸ J. M. Tedder, *J. Chem. Soc.* p. 4003 (1957).

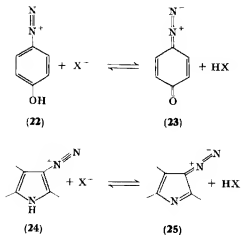
⁹ J. M. Tedder and G. Theaker, *J. Chem. Soc.* p. 4008 (1957).

¹⁰ J. M. Tedder and G. Theaker, *J. Chem. Soc.* p. 2573 (1958).

¹¹ H. P. Patel and J. M. Tedder, *J. Chem. Soc.* p. 4889 (1963).

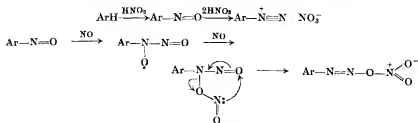
¹² J. M. Tedder and B. Webster, *J. Chem. Soc.* p. 3270 (1960).

¹³ H. P. Patel, Ph.D. Thesis, University of Sheffield, 1963.



showed that such compounds could be converted into 2-diazopyrroles.¹⁴ This was the first synthesis of this class of compound and in view of the known instability of 2-aminopyrroles it may well prove to be the only route. Certainly the only reported reactions of unstable 2-aminopyrroles with nitrous acid led to decomposition.¹⁵ The technique of the direct introduction of the diazonium group has also been successfully applied to indoles and pyrazoles^{15a} (see also footnotes 22 and 29).

The reactions involve the initial formation of the nitroso compound which reacts further with the nitrous acid present to yield the diazonium nitrate. The reaction has been shown to involve exactly 3 moles of nitrous acid and the mechanism is probably as follows:¹⁶



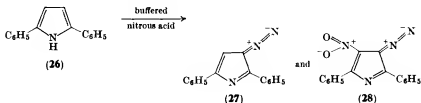
¹⁴ J. M. Tedder and B. Webster, *J. Chem. Soc.* p. 1638 (1962).

¹⁵ H. Fischer, H. Guggemos, and A. Schafer, *Ann. Chem.* **540**, 45 (1939).

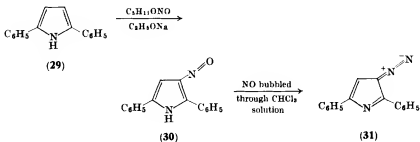
^{15a} H. P. Patel, J. M. Tedder, and B. Webster, *Chem. Ind. (London)* p. 1163 (1961).

¹⁶ J. M. Tedder and G. Theaker, *Tetrahedron*, **5**, 288 (1959).

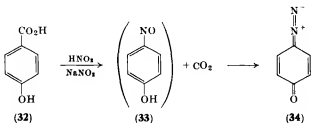
With molecules as reactive as pyrroles, nitrate ions lead to nitration, and treatment of 2,5-diphenylpyrrole (**26**) with nitrous acid yielded the 3-diazo-4-nitro-2,5-diphenylpyrrole (**28**) as well as the expected 3-diazo-2,5-diphenylpyrrole (**27**).¹²



The nitration was avoided by employing a two-step process. The pyrrole (**29**) was converted into 3-nitroso-2,5-diphenylpyrrole by treatment with pentylnitrite and sodium ethoxide. The resulting nitroso compound was converted into the diazo compound (**31**) by treatment with gaseous nitric oxide. Exactly the same problem was encountered in the preparation of 2-diazo-3,5-diphenylpyrrole.¹²

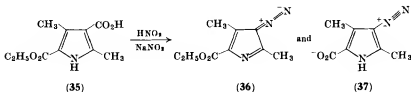


Treatment of *o*- or *p*-hydroxybenzoic acids with buffered nitrous acid resulted in the decarboxylation of the acid and the introduction of a



nitroso group or a diazonium group in the site originally occupied by the carboxyl group.¹⁷

The same reaction has been applied to a pyrrole carboxylic acid (35) and although some diazo compound (36) was formed the reaction



was complicated by side reactions and the yield was too small for this to be considered as a practicable method of preparing diazo compounds.¹⁴

An obvious alternative route to heterocyclic diazo compounds would be that employed by Doering and De Puy for the synthesis of diazocyclopentadiene. However, attempts to do this have not been very successful.¹⁸

III. Heterocyclic Diazo Compounds

A. DIAZOPYRROLES

Diazopyrroles are stable yellow crystalline solids. They are light-sensitive and decompose on heating but they can be kept indefinitely in the cool and dark. They are weak bases, forming relatively stable diazonium salts with strong acids, which can be isolated as crystalline solids. Soluble in organic solvents such as acetone, ethanol, or chloroform, diazopyrroles are insoluble in water. There is a very marked difference in the stability of the 3-diazopyrroles and the 2-diazopyrroles. The former require no special precautions in handling but the latter, although stable once crystalline, decompose slowly in solution.

The yellow diazopyrroles have an absorption maximum in the region 320–400 $m\mu$ (extinction coefficient varying greatly, depending on the other substituents in the pyrrole ring) in their ultraviolet spectra and all show the characteristic diazo peak (2080–2180 cm^{-1}) in their infrared spectra. In general the infrared diazo absorption



¹⁷ J. M. Tedder and G. Theaker, *J. Chem. Soc.* p. 257 (1959).

¹⁸ B. Webster, Ph.D. Thesis, University of Sheffield, 1961.

occurs at slightly shorter wavelengths for the 2-diazopyrroles than for the corresponding 3-diazo compounds (see Table I).

TABLE I

SPECTRAL CHARACTERISTICS OF SOME TYPICAL DIAZOPYRROLES^{12, 14}

								
R ₁	R ₂	R ₃	M.p. (°C)	ν_{\max} (cm ⁻¹)	λ_{\max} (m μ)	M.p. (°C)	ν_{\max} (cm ⁻¹)	λ_{\max} (m μ)
C ₆ H ₅	H	C ₆ H ₅	104	2138	345	122	2095	387
C ₆ H ₅	NO ₂	C ₆ H ₅	116.5	2172	—	145	2150	339
CH ₃ CO	C ₆ H ₅	CH ₃	102	2146	351	—	—	—
C ₆ H ₅	H	CH ₃	—	—	—	81	2062	360
CH ₃	CH ₃	CO ₂ Et	—	—	—	79.5-80	2155	333

Although a preliminary study of the effect of light on 3-diazo-2,4,5-triphenylpyrrole (**21**) has been reported, the products of photolysis have not been identified.^{18a}

Diazopyrroles will not, of course, couple with phenols or phenolate anions. Pyrrole diazonium salts are too weakly reactive to couple with phenols and in aqueous alkali necessary for phenolate anions to be present the insoluble diazopyrrole is precipitated. A dilute acid solution of 3-diazopyrrole and phloroglucinol showed no signs of coupling even after a month. However, heating a diazopyrrole with a phenol (either fusing them together, or better refluxing a solution of them in an organic solvent, e.g., chloroform) results in the formation of the corresponding azo dye. Presumably there is some proton transfer from the phenol to the diazopyrrole, so that the phenolate anion and the pyrrole diazonium salt are formed together and then couple immediately.¹²

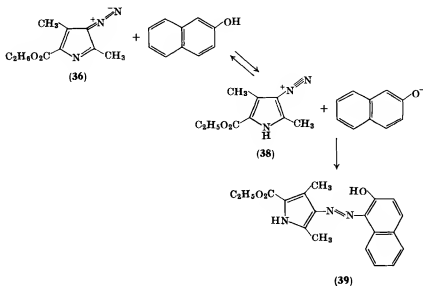
There is a report in the literature of the diazotization of ethyl 4-amino-3,5-dimethylpyrrole-2-carboxylate to yield a diazonium salt which couples with alkaline β -naphthol.^{19, 20} However, the experi-

^{18a} F. Angelico, *Atti. Reale Accad. Lincei* **17**, 655 (1908).

¹⁹ H. Fischer and A. Stern, *Ann. Chem.* **446**, 240 (1926).

²⁰ H. Fischer and K. Zeile, *Ann. Chem.* **483**, 257 (1930).

mental section of this paper²⁰ clearly describes the formation of a brown precipitate when the coupling was carried out in sodium bicarbonate solution. When the product was recrystallized from chloroform the solution turned red and the correct azo dye was obtained. Repetition of this work confirmed the experimental observations in every detail. However, the initial brown precipitate was in fact the diazopyrrole and β -naphthol coprecipitated. Almost all the coupling takes place in the "recrystallization" procedure (36-39).



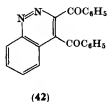
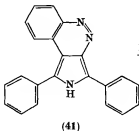
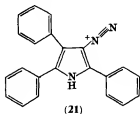
The azo dyes are typical red crystalline compounds; those derived from 2-diazopyrroles (40) form lakes with the transition metals.¹⁴

Although attempts to make pyrrole diazonium salts couple intermolecularly have been unsuccessful, 3-diazo-2,4,5-triphenylpyrrole (21) on prolonged heating in dilute sulfuric acid undergoes internal coupling (21→41).²¹ That coupling occurred with the phenyl group in the 4-position rather than the 2-position is shown by the formation of the diketone (42) on oxidation with nitric acid.

²¹ F. Angelico and F. Monforte, *Gazz. Chim. Ital.* **53**, 795 (1923).



Possible structure of complex formed between transition metal cations and azo dyes derived from 2-diazopyrroles.



B. DIAZOINDOLES

Diazoindoles are very similar in their properties to diazopyrroles (see Table II). 3-Diazoindoles are stable crystalline compounds sensitive to light and forming stable diazonium salts with strong acids. 3-Diazoindoles cannot be prepared by the direct reaction of the indole with nitrous acid, presumably because the nitroso compound (43) completely rearranges to the oximoimine form (44).²² (See p. 12.)

3-Diazoindoles will couple with phenols under the same conditions as those described for diazopyrroles. The benzindoles were very much

²² H. P. Patel and J. M. Tedder, *J. Chem. Soc.* p. 4593 (1963).

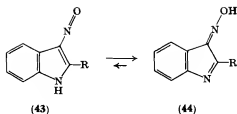


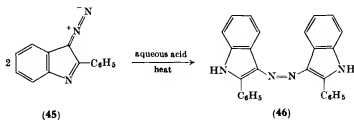
TABLE II

SPECTROSCOPIC PROPERTIES OF SOME TYPICAL DIAZOINDOLES²²

Diazindazole	M.p. (°C)	ν_{\max} (cm ⁻¹)	λ_{\max} (m μ)
3-Diazo-2-phenylindole	108 (115)	2120	350 (ϵ = 11,600)
3-Diazo-2-(<i>p</i> -methoxyphenyl)indole	116	2085	347 (ϵ = 9300)
3-Diazo-5-methoxy-2-(<i>p</i> -methoxy-phenyl)indole	138	2100	346 (ϵ = 4000)
3-Diazo-2-phenyl-6,7-benzindole	167	2100	367.9 (ϵ = 7700)
3-Diazo-2-phenyl-4,5-benzindole	143	2085	359 (ϵ = 6500)

less reactive and 3-diazo-2-phenyl-4,5-benzindole would not couple with β -naphthol when the two were fused together at 130° for an hour.²²

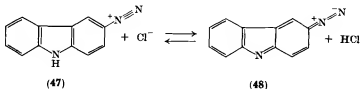
3-Diazo-2-phenylindole (**45**) when heated with aqueous acid does not undergo intramolecular coupling like triphenyldiazopyrrole (**21**) but instead undergoes an intermolecular coupling with the elimination of nitrogen²³:



²³ V. Castellana and A. d'Angelo, *Atti Reale Accad. Lincei* **14**, 145 (1905).

C. 3-DIAZOCARBAZOLE

In 1901 Ruff and Stein obtained carbazole-3-diazonium chloride by the diazotization of 3-aminocarbazole.²⁴ They reported that treatment of a cold solution of the diazonium chloride (47) with concentrated sodium hydroxide yielded a red compound, which when analyzed gave inexplicable results. Subsequent work by Morgan and Read showed that a very unstable diazo compound (48) could be obtained.²⁵ The diazo compound was far less stable than either the



diazopyrroles or the diazoindoles.²⁶ It coupled instantly with β -naphthol, and treatment of an aqueous solution of the diazonium chloride with alkaline β -naphthol led to immediate coupling and precipitation of the azo dye. In this connection, in unreported experiments the present reviewer found that diazotization of 5-aminoindole yielded a diazonium salt but no stable diazo compound when the aqueous solution was treated with alkali.

D. DIAZOPYRAZOLES

In 1896 Knorr and Stolz succeeded in diazotizing 4-amino-1-phenyl-2,3-dimethylpyrazole and so obtained the first diazonium salt with a pyrazole nucleus.²⁶ Much later, Morgan and Reilly diazotized 4-amino-3,5-dimethylpyrazole and studied the reactions of the resultant diazonium salt (49).^{27, 28} In aqueous solution it coupled with β -naphthol and the crystalline diazonium chloride was quite stable. However, these workers did not isolate the free diazo compound. The diazo compounds can be readily obtained by treating the

²⁴ O. Ruff and V. Stein, *Ber. Deut. Chem. Ges.* **34**, 1668 (1901).

²⁵ G. T. Morgan and H. N. Read, *J. Chem. Soc.* p. 2709 (1922).

²⁶ L. Knorr and F. Stolz, *Ann. Chem.* **293**, 68 (1896).

²⁷ G. T. Morgan and J. Reilly, *J. Chem. Soc.* **103**, 808 (1913).

²⁸ G. T. Morgan and J. Reilly, *J. Chem. Soc.* p. 439 (1914).

aqueous solutions of the diazonium salts with alkali.^{7, 29-31} The diazo compounds are in some cases soluble in water and are best obtained by extraction with organic solvents (see Table III).

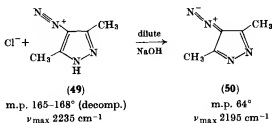


TABLE III

SPECTROSCOPIC PROPERTIES OF SOME TYPICAL DIAZOPYRAZOLES^{7, 29, 31}

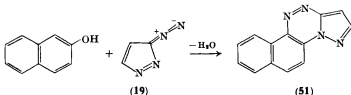
Diazopyrazole	M.p. (°C)	ν _{max} (cm ⁻¹)	λ _{max} (mμ)
3-Diazopyrazole	—	2130	270
3-Diazo-5-benzoyl-4-phenylpyrazole	100 (decomp.)	2140	272
3-Diazo-5-benzyl-4-phenylpyrazole	Unstable	2120	—
4-Diazo-3,5-dimethylpyrazole	64	2195	—
4-Diazo-3,5-diphenylpyrazole	224	2189	354
4-Diazo-5(3)-ethoxy-3(5)-methylpyrazole	Oil	2120	—
4-Diazo-3-benzyl-5-phenylpyrazole	Infusible below 300	2120	—
4-Diazo-3-benzoyl-5-phenylpyrazole	148	2190	—

The 3(5)-diazopyrazoles are noticeably less stable than the 4-diazo compounds.³¹ Both are light-sensitive and both couple with phenols in organic solvents. The dyes so obtained form lakes with transition metal ions (cf. dyes from 2-diazopyrroles above, e.g., 40).¹³ The coupled product from 3-diazopyrazole and β-naphthol is not in fact the simple azo dye but a condensation product derived from it.⁷

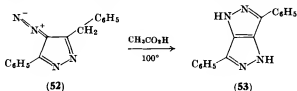
²⁹ H. P. Patel and J. M. Tedder, *J. Chem. Soc.* p. 4589 (1963).

³⁰ D. G. Farnum and P. Yates, *Chem. Ind. (London)* p. 659 (1960).

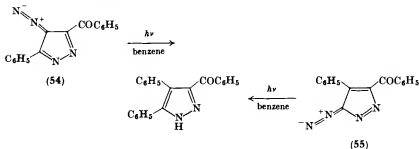
³¹ D. G. Farnum and P. Yates, *J. Am. Chem. Soc.* **84**, 1399 (1962).



4-Diazo-3-benzyl-5-phenylpyrazole (52) undergoes an intramolecular coupling between the diazo group and the methylene group.³¹



Photolysis of 4-diazo-3-benzoyl-5-phenylpyrazole (54) and of 3-diazo-5-benzyl-4-phenylpyrazole (55) in benzene solution led to the evolution of nitrogen and the formation in both cases of 3-benzoyl-4,5-diphenylpyrazole.³¹ Photolysis of the 4-diazo derivative (54) in



aqueous acetone gave the 4-hydroxy compound, and photolysis in acetic acid gave the 4-acetoxy compound. However, similar photolysis of the 3(5)-diazo compound (55) in aqueous acetone resulted in the loss of nitrogen to yield 3-benzoyl-4-phenylpyrazole.³¹

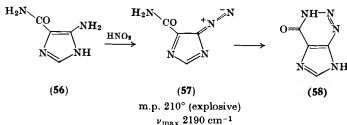
E. DIAZOINDAZOLE

Bamberger's original preparation of diazoindazole has already been referred to and most of the work on this compound is Bamberger's.¹ The physical properties of the crystalline compound (m.p. 106°, ν_{\max}

2120 cm^{-1}) are similar to those of the diazopyrazoles. Like them it is soluble in most organic solvents (except petroleum) and is moderately soluble in water. It readily forms stable diazonium salts with strong acids. The diazo compound (as well as the diazonium salt) couples with β -naphthol and N,N -dimethylaniline. The dye formed from β -naphthol readily loses water when warmed in amyl alcohol, yielding a compound presumably having a structure analogous to that obtained when 3-diazopyrazole couples with β -naphthol (see **51** above).¹

F. DIAZOIMIDAZOLE

Diazoimidazoles do not appear to have received very extensive study. The only fully authenticated diazoimidazole appears to be 5-diazoimidazole-4-carboxamide (**57**).³² Few reactions have been reported for this compound beyond its cyclization to 2-azahypoxanthine (**58**).



G. DIAZOPURINES

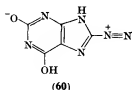
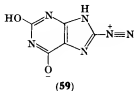
Diazotization of some 8-aminopurines has been reported to yield stable diazopurines. Gomberg reported that diazotization of 8-aminocaffeine yielded a very unstable "diazocaffeine."³³ Later, Hans Fischer described crystalline 8-diazoxanthine and 8-diazotheophylline.³⁴ He proposed the same four-membered ring structure for the diazo group that Bamberger originally suggested in his structure of diazoindazole (**1**). These compounds have recently been reinvestigated and it has been suggested that they have the same diazo

³² Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.* **26**, 2396 (1961).

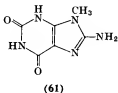
³³ M. Gomberg, *Am. Chem. J.* **23**, 51 (1901).

³⁴ H. Fischer, *Z. Physiol. Chem.* **60**, 69 (1909).

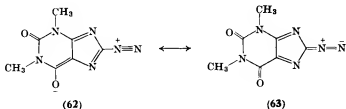
structure as the compounds discussed above.^{35,36} However, their stability could also be due to contributions from a zwitterion structure (**59** and **60**) as with diazooxides.



Jones and Robins claimed to have excluded this possibility by preparing 8-amino-9-methylxanthine (**61**).³⁵ This compound did not



yield a stable diazo compound. However, this argument does not rule out the importance of zwitterionic structures; for example, 8-diazotheophylline can be represented as a hybrid of structures (**62** and **63**).



There is strong spectroscopic evidence that **62** is the predominant canonical form. The triple-bond infrared absorption for these compounds is in the diazonium salt range (i.e., diazothetheophylline, $\nu_{\max} = 2225 \text{ cm}^{-1}$; diazoxanthine, $\nu_{\max} = 2250\text{--}2400 \text{ cm}^{-1}$). Their general properties and chemical behavior are much more akin to those

³⁵ J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.* **82**, 3773 (1960).

³⁶ G. A. Usbeck, J. W. Jones, and R. K. Robins, *J. Am. Chem. Soc.* **83**, 1113 (1961).

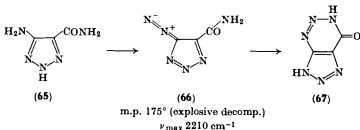
of diazooxides. Structure **63** will, of course, make some contribution to the ground state of these molecules, but it seems better to regard them as diazooxides and they will for this reason receive no further discussion here.

H. DIAZOTRIAZOLES AND DIAZOTETRAZOLE

5-Aminotetrazole on treatment with nitrous acid in *dilute* aqueous solution yields a diazonium salt which undergoes the usual coupling reactions.³⁷ On treatment with alkali the solution becomes yellow and probably diazotetrazole is present. However, if the reaction is carried out in moderately concentrated solution, an explosive mixture is obtained! The reviewer has had dramatic, if harmless, experience of this system. After one originally mild explosion had shattered the reaction vessel, the solution, now scattered about the room and the experimenter, produced small detonations for the next 4 hours! The very formula of the compound explains its instability (**64**).



There is one report of a diazotriazole.³² Diazotization of 5-amino-1,2,3,4-tetrazole-4-carboxamide (**65**) with pentynitrite in acetic acid yielded 5-diazotriazole-4-carboxamide (**66**). The one reaction reported for this compound was its cyclization to yield 2,8-diazahypoxanthine (**67**).



IV. Applications of Heterocyclic Diazo Compounds

The light-sensitive properties of heterocyclic diazo compounds have been utilized for two different photoreproduction processes. The first

³⁷ J. Thiele, *Ann. Chem.* **270**, 46 (1892).

of these is a lithographic process.³⁸ The heterocyclic diazo compound is deposited upon a suitable metal or plastic surface; the coated plate is exposed to light. The photolysis products and the original diazo compound have different solubilities and the image is developed by treatment with a suitable solvent. This image, which is described as highly ink- and grease-receptive, is used in offset printing.

The second process is a so-called "dye-line" process.^{39, 40} The heterocyclic diazo compound and a phenol are coated together on paper together with various additional compounds to prevent "fogging" of the image. The tracing to be copied is then placed on top and illuminated with ultraviolet light. The lines of the tracing cast a shadow and prevent the diazo compound being decomposed directly underneath them; elsewhere the diazo compound is destroyed. The coated paper is then removed and heated, under which conditions the diazo compound couples with the phenol, producing an image of the original drawing. This process is intended to be an improvement on the conventional "dye-line" photocopying processes in which ordinary stabilized diazonium salts are used and in which coupling is induced by chemical methods (i.e., by rendering the paper alkaline either by washing it with alkali or by exposing it to ammonia vapor).

³⁸ British Patent 816,382; *Chem. Abstr.* **55**, 188 (1961).

³⁹ British Patent 977,326; *Chem. Abstr.* **62**, 6607 (1965).

⁴⁰ British Patent 988,221; *Chem. Abstr.* **62**, 15636 (1965).

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The Chemistry of Diazepines

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A. CATALA NOBLE

E. I. duPont de Nemours and Company, Inc., Wilmington, Delaware

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I. Introduction

The aim of this review is to attempt to collect in one place the large volume of work which deals with the chemistry of seven-membered heterocyclic compounds containing two nitrogen atoms. With the exception of a review ^{1,2} in Polish which appeared during the preparation of this manuscript, the field of diazepines has not been the subject of any review. For this reason, although emphasizing the more recent work, the present review also includes older background material. To a large extent the recent interest in this field is due to the discovery of materials with medicinal activity such as chlordiazepoxide.

¹ A. Nawojski, *Wiadomości Chemiczne* **12**, 673 (1964).

² A. Nawojski, *Wiadomości Chemiczne* **19**, 75 (1965).

In this review the literature through early 1966 has been covered. Synthetic methods leading to the various diazepine ring systems are summarized and the reactions and properties that have been studied for these ring systems have been discussed. For convenience the sections are divided into diazepines with nitrogen atoms in the 1,2-, 1,3-, and 1,4-positions. These sections are then further divided by taking into account rings (if any) fused to the diazepine. All seven-membered heterocyclic compounds containing two ring nitrogens are considered under this outline regardless of the degree of unsaturation.

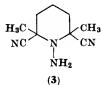
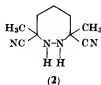
II. 1,2-Diazepines

A. SIMPLE MONOCYCLIC COMPOUNDS

1. *Synthesis*

The parent hexahydro-1,2-diazepine (**1**, R = H) has been prepared.³ Condensation of 1,2-dicarbethoxyhydrazine and 1,5-dibromopentane in dimethylformamide in the presence of potassium gave **1** (R = CO₂Et) which could be hydrolyzed to **1** (R = H). The 1,2-dibenzoyl- and 1,2-bis(anilinoformyl) derivatives of **1** were also prepared.³ In a similar manner the dilithium derivative of hydrazobenzene and 1,5-diiodopentane gave **1** (R = C₆H₅).⁴

Overberger and co-workers originally reported⁵ that heptane-2,6-dione, hydrazine sulfate, and sodium cyanide gave the diazepine (**2**); however, it was later shown⁶ that the work on the preparation⁵ and oxidation⁷ of this compound was in error and that the product was the aminopiperidine (**3**).



³ G. Zinner and W. Deucker, *Arch. Pharm.* **295**, 526 (1962).

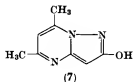
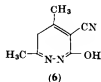
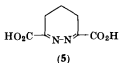
⁴ G. Wittig, W. Joos, and P. Rathfelder, *Ann. Chem.* **610**, 180 (1957).

⁵ C. G. Overberger, T. B. Gibb, Jr., S. Chibnik, P. T. Huang, and J. J. Monagle, *J. Am. Chem. Soc.* **74**, 3290 (1952).

⁶ C. G. Overberger and B. S. Marks, *J. Am. Chem. Soc.* **77**, 4097 (1955).

⁷ C. G. Overberger, P. T. Huang, and T. B. Gibb, Jr., *J. Am. Chem. Soc.* **75**, 2082 (1953).

The condensation of a variety of 1,3-diarylpropanes with hydrazine gave 63–98% yields of 3,7-diaryl-5,6-dihydro-4*H*-1,2-diazepines (**4**, R=H).⁸ It had originally been reported⁹ that 1,3,5-triphenyl-1,5-pentanedione and hydrazine hydrate gave 2,4,6-triphenyl-1-amino-1,4-dihydropyridine; however, Carpino¹⁰ has shown that the product was the diazepine (**4**, R=Ar=C₆H₅). In a similar manner **5** was obtained from α,α' -dioxopimelic acid.¹¹ The reaction of acetylacetone with cyanoacetylhydrazide in ethanol containing acetic acid gave a monoacetylhydrazone that was reported to give diazepine (**6**).¹² Later, however, this product was shown^{13,14} to have structure **7**.



The diazepinol (**8**) has been obtained by treatment of *O*-ethyl-nitroso-*N,N*-pentamethyleneimmonium fluoroborate (**9**) with cold 1.5 *N* sodium carbonate.¹⁵

2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (**10**) has been prepared^{16,17} by mild acid treatment of **11**, **12**, or the intermediate bicyclic ketone (**13**) with very dilute acid or alkali.¹⁷ In a

⁸ M. Lipp, F. Dallacker, and S. Munnes, *Ann. Chem.* **618**, 110 (1958).

⁹ K. W. Merz and H. Richter, *Arch. Pharm.* **275**, 294 (1937).

¹⁰ L. A. Carpino, *J. Org. Chem.* **30**, 736 (1965).

¹¹ E. E. Blaise and H. Gault, *Bull. Soc. Chim. France* [4], **1**, 83 (1907).

¹² W. Ried and E. U. Kocher, *Angew. Chem.* **70**, 164 (1958).

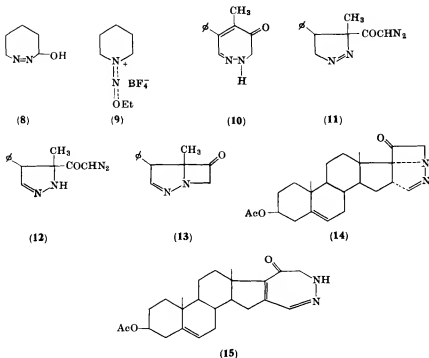
¹³ W. Ried and E. U. Kocher, *Ann. Chem.* **631**, 185 (1960).

¹⁴ W. Ried and E. U. Kocher, *Ann. Chem.* **647**, 116 (1961).

¹⁵ S. Huenig, L. Geldern, and E. Luecke, *Rev. Chim. Acad. Rep. Populaire Roumaine* **7**, 935 (1962).

¹⁶ J. A. Moore, *J. Am. Chem. Soc.* **77**, 3417 (1955).

¹⁷ J. A. Moore and R. W. Medeiros, *J. Am. Chem. Soc.* **81**, 6026 (1959).



similar manner the compound **14**, obtained from 3 β -acetoxy-5,16-etiadienyl chloride,¹⁸ can be isomerized to the diazepine (**15**).¹⁹

It might be noted that compounds such as **13**, **14**, and **16**²⁰ can be considered to be bridged diazepines.

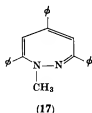
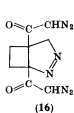
2,4,6-Triphenylthiapyrylium salts react smoothly with methylhydrazine to give **17** and with hydrazine to give 3,5,7-triphenyl-4*H*-1,2-diazepine (**18**, R = C₆H₅).²¹ The corresponding compound [**18**, R = *p*-(CH₃)₂N—C₆H₄] was also prepared. The possibility of the compounds having other structures was eliminated through spectral studies.

¹⁸ J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Am. Chem. Soc.* **84**, 390 (1962).

¹⁹ J. A. Moore and L. J. Pandya, *J. Org. Chem.* **29**, 336 (1964).

²⁰ F. B. Kipping and J. J. Wren, *J. Chem. Soc.* p. 1733 (1957).

²¹ E. Klingsberg, *Abstr. Am. Chem. Soc. Meeting, Sept., 1965*, p. 66S (1965).



2. Reactions

The 1,2-diphenylhexahydrodiazepine (**1**, $R = C_6H_5$) has been subjected to the conditions of the benzidine rearrangement to yield **19**.⁴

The lithium aluminum hydride reduction of **4** ($R = H$, $Ar = C_6H_5$) was originally reported²² to give **20** but this was later shown²³ to probably be **21** which resisted oxidation by mercuric oxide. Reduction of **4** ($R = H$, $Ar = C_6H_5$) with palladium on carbon also gave **21**, while reduction with 2 moles of hydrogen gave **20** which was immediately oxidized with mercuric oxide to give **22**.^{23, 24} All attempts to work with **20** resulted in air oxidation to **21**. Isomerization of **22** to **21** takes place in ethanol at room temperature. The thermal decomposition of **22** is 100-fold faster than that of linear *trans*-azo-1-phenylethane indicating a *cis* configuration of the azo linkage in **22** which makes it less stable than the linear *trans*-azo compound.^{23, 24} The products of the thermal decomposition are those expected from the intermediate biradical (**23**). Dipole moment studies²⁵ on **4** ($Ar = C_6H_5$, $R = H$) confirm the *cis* configuration of the seven-membered ring azo compound. Solid state photolysis of (**22**) gave *cis*-1,2-diphenyleyclopentane.^{25a}

Reaction of **4** ($R = H$, $Ar = C_6H_5$) with *N*-bromosuccinimide or, more cleanly, with *N*-chlorosuccinimide gave 4-methyl-3,6-diphenylpyridazine (**24**, $R = CH_3$).²⁶ Two possible mechanisms for the formation of **24** imply that carbon 5 is extruded in the ring contraction.

²² C. G. Overberger and J. J. Monagle, *J. Am. Chem. Soc.* **78**, 4470 (1956).

²³ C. G. Overberger and J. G. Lombardino, *J. Am. Chem. Soc.* **80**, 2317 (1958).

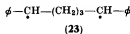
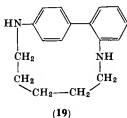
²⁴ C. G. Overberger, J. G. Lombardino, I. Tashlick, and R. G. Hiskey, *J. Am. Chem. Soc.* **79**, 2662 (1957).

²⁵ C. G. Overberger, J. P. Anselme, and J. R. Hall, *J. Am. Chem. Soc.* **85**, 2752 (1963).

^{25a} C. G. Overberger and C. Yaroslavsky, *Tetrahedron Letters*, 4395 (1965).

²⁶ R. G. Amiet, R. B. Johns, and K. R. Markham, *Chem. Commun.* p. 128 (1965).

This was confirmed by treating **4** ($R = CH_3$, $Ar = C_6H_5$) with *N*-chlorosuccinimide to give **24** ($R = C_2H_5$) and **24** ($R = CHClCH_3$). When **4** ($R = Ar = C_6H_5$) was treated in the same way, **24** ($R = CH_2C_6H_5$), **24** ($R = CHClC_6H_5$), and a small amount of **24** ($R = CCl_2C_6H_5$) were



obtained. If the reaction was stopped when the solution was at its maximal yellow color, compound **25** was isolated together with unreacted **4** and **24**. Compound **25** is converted to **24** by hydrogen chloride in ethanol.²⁶ The isolation of **25** and its conversion to **24** indicates that the ring contraction of **4** to **24** proceeds through such an intermediate.

Treatment of **8** with mild acid gave **26** which on stronger treatment with hydrochloric acid undergoes ring contraction to **27**.¹⁵

The reactions of diazepinone (**10**) have been rather extensively studied²⁷⁻³⁶ and a summary of some of the reactions has appeared.³⁷

²⁷ R. K. Bly, E. C. Zoll, and J. A. Moore, *J. Org. Chem.* **29**, 2128 (1964).

²⁸ J. A. Moore and J. Binkert, *J. Am. Chem. Soc.* **81**, 6029 (1959).

²⁹ J. A. Moore and C. L. Habraken, *J. Org. Chem.* **30**, 1889 (1965).

³⁰ J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.* **31**, 34 (1966).

³¹ J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *J. Am. Chem. Soc.* **84**, 3022 (1962).

³² J. A. Moore, R. W. Medeiros, and R. L. Williams, *J. Org. Chem.* **31**, 52 (1966).

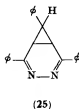
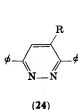
³³ J. A. Moore and W. J. Theuer, *J. Org. Chem.* **30**, 1887 (1965).

³⁴ J. A. Moore and E. C. Zoll, *J. Org. Chem.* **29**, 2124 (1964).

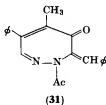
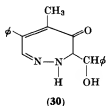
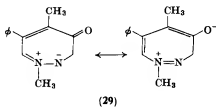
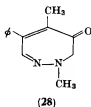
³⁵ W. J. Theuer and J. A. Moore, *Chem. Commun.* p. 468 (1965).

³⁶ R. L. Wineholt, E. Wyss, and J. A. Moore, *J. Org. Chem.* **31**, 48 (1966).

³⁷ J. A. Moore, *Trans. N.Y. Acad. Sci.* [2], **27**, 591 (1965).

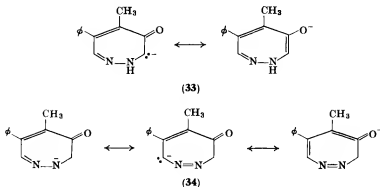


Methylation with dimethyl sulfate in alkali gave the methyl derivatives **28** and **29**. Although formaldehyde attacks at N-2, aldol condensation of **10** with benzaldehyde gave the 3 α -hydroxybenzyl compound (**30**) which is dehydrated to the 2-acetyl-3-benzylidene compound (**31**) with acetic anhydride.²⁷ With acid anhydrides the 2-acyl derivatives are obtained; however, with acid chlorides in pyridine or dimethylaniline the bicyclic ketone (**32**) is formed.³¹ Despite the occurrence of the bicyclic product (**32**) and the bicyclic intermediate (**13**) there is no evidence for the existence of a bicyclic tautomer of **10**.³⁷



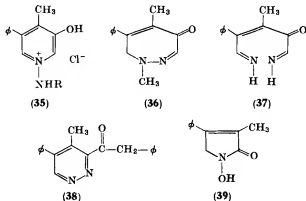
Deuteration of the anions **33** and **34** formed from **10** in basic medium showed that deuterium exchange occurs at C-3 and more slowly at C-7 to give the 3,3,7- d_3 product.³⁴

Oxidation of the diazepinone (**10**) with hydrogen peroxide gave 5-methyl-4-phenylpyrazole-1-acetic acid.²⁹ This reaction is probably a result of transannular attack of N-2 at C-5.



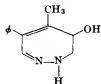
With hydrochloric acid **10**²⁸ and **29**³³ undergo ring contraction in good yield to the 1-amino-3-hydroxypyridinium compounds (**35**). This reaction involves extrusion of N-1 and does not occur with **28**. 1-Acylaminopyridinium compounds arise from the bicyclic ketone (**32**) under the same conditions. A different type of pyridine derivative is obtained by reaction of **10**,³⁴ **28**, or **36**³³ with base. Thus **10** gave a mixture of 2- and 6-amino-3-hydroxy-4-methyl-5-phenylpyridine, while **28** gave the former and **36** the latter product. The formation of the pyridines can be accounted for by cyclization of **37** which could be formed via a β elimination from the enolide anion (**33**).

Hydrolysis of **31** led to rearrangement with extrusion of C-3 to give the pyridazine (**38**).²⁷ Another example of this transformation occurs when **36** is treated with acid to give 1,4-dimethyl-5-phenyl-1,6-dihydropyridazine-3-carboxaldehyde.³³



Although the diazepinone (**10**) gave a normal semicarbazone, treatment of **10** or **28** with buffered hydroxylamine gave the cyclic hydroxamic acid (**39**).²⁸ The *N*-acyl derivative of **10** also reacts with hydroxylamine but in this case the product is either a bicyclic or tricyclic iminohemiketal.²⁸

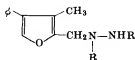
The diazepinol (**40**) is readily obtained from ketone (**10**) with sodium borohydride and is converted back into **10** with *N*-bromoacetamide or by Oppenauer oxidation.³² In a similar manner **32** and the *N*-acetyl derivative of **10** can be reduced to carbinols. Acylation of **40** or treatment of the reduction product of **32** with acetic acid gave the transannular oxide (**41**). The carbinol (**40**), the acetyl carbinol from **10**, the oxide (**41**), and the diacetyl analog of **41** all undergo rearrangement with mineral acid to give the four furfuryldiazines (**42**).³²



(40)



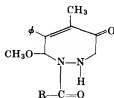
(41)



(42)

The 7-methoxy-1-acetyl and 1-benzoyl tetrahydrodiazepinones (**43**) have been prepared by reaction of **10** with an acid chloride and pyridine in methanol or from **32** by treatment with acidic methanol.³⁰ These compounds (**43**) undergo base-catalyzed rearrangement to 5-methoxy-3-methyl-4-phenyl-2-pyrrolealdehyde.³⁶ The formation of this pyrrole can be explained through an alternative cyclization of an intermediate of the type **37**.

In addition to the above-mentioned ring contractions and transannular bonding of compounds of the type **10** in ionic reactions, photo-induced valence tautomerism has also been noted.³⁵ Thus **10** or the various 2-substituted compounds can be converted to **44**.³⁵



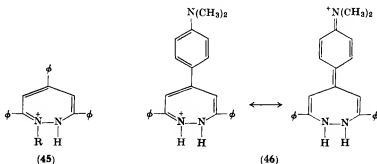
(43)



(44)

The steroidal diazepine (**15**) differs greatly in reactivity from **10** and fails to undergo the characteristic ring contractions and transannular reactions of the latter.¹⁹ A number of reactions of the precursor **14** have, however, been reported.³⁸

Protonation of the triaryl-1,2-diazepines (**17** and **18**) gave cations (**45**).²¹ In the case of **18** [$R = p\text{-(CH}_3)_2\text{N-C}_6\text{H}_4$] the compound is diprotonated and the effect of this on the ultraviolet spectrum implies planarity in the parent diazepine. It is also possible to monoprotonate the compound **18** [$R = p\text{-(CH}_3)_2\text{N-C}_6\text{H}_4$] and the deeply colored cation suggests aromatic resonance (**46**) for the diazepinium salt.²¹



7-Methyl-2,5-diphenyl-3,4-diazanorcaradiene is believed to be in equilibrium with a small amount of the corresponding diazepine.^{38a}

B. BENZO COMPOUNDS

1. Synthesis

The simple 1,2,3,4-tetrahydro-5*H*-2,3-benzodiazepine (**47**) and 3,4-dihydro-5*H*-2,3-benzodiazepine (**48**) have been prepared.³⁹ Thermal decomposition of **49** yielded the dihydro compound (**48**) which was catalytically reduced to **47**. Compound **47** was also obtained by basic cleavage of the diazepine (**50**), which was prepared by reaction of phthaloyl hydrazide and *o*-chloromethyl-2-phenylethyl chloride.³⁹ Compound **49** was prepared from the diaziridine (**51**, $R = \text{H}$) which together with **51** ($R = \text{CH}_3$)^{40, 41} can be considered as bridged 1,2-

³⁸ T. Yamachi and J. A. Moore, *J. Org. Chem.* **31**, 42 (1966).

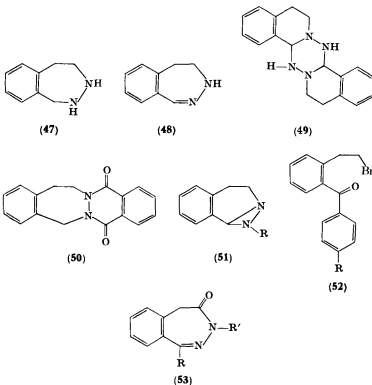
^{38a} G. Maier, *Chem. Ber.* **98**, 2446 (1965).

³⁹ E. Schmitz and R. Ohme, *Chem. Ber.* **95**, 2012 (1962).

⁴⁰ E. Schmitz, *Angew. Chem.* **71**, 127 (1959).

⁴¹ E. Schmitz, *Chem. Ber.* **95**, 676 (1962).

diazepine derivatives. A number of substituted analogs of **48** have been prepared by the reaction of benzophenones (**52**) with hydrazines.⁴²



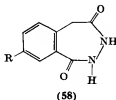
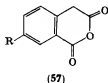
Dehydration of *o*-acetylphenylacetic acid phenylhydrazone gave diazepine (**53**, $R = CH_3$, $R' = C_6H_5$) and 1-methyl-2-(phenylamino)-3(2*H*)isoquinoline.⁴³ Pyrolytic dehydration gave **53** as the major product while sulfuric acid gave the quinoline as the major product. The azine of *o*-acetylphenylacetic acid on pyrolysis gave the diazepine (**53**, $R = CH_3$, $R' = H$) which was also obtained by pyrolytic elimination of carbamic acid from *o*-acetylphenylacetic acid semicarbazone.⁴³ Similar pyrolysis of *o*-formylphenylacetic acid semicarbazone gave **53** ($R = R' = H$). These last two diazepines are assigned structure **53**

⁴² C. Van der Stelt and W. T. Nauta, *Rec. Trav. Chim.* **84**, 640 (1965).

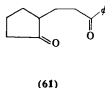
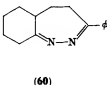
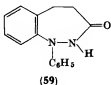
⁴³ J. O. Halford, R. W. Raiford, Jr., and B. Weissman, *J. Org. Chem.* **26**, 1898 (1961).

on the basis of the close similarity of their infrared and ultraviolet spectra to those of the *N*-phenyl compound. The possibility of the 1*H* form has not, however, been excluded.

Diazepine (54, R = H) was obtained by the action of hydrazine on 55 or 56.⁴⁴⁻⁴⁶ Reaction of phenylhydrazine with 55 or 56 gave 54, (R = C₆H₅).⁴⁷ In a similar manner 57 (R = H or NO₂) with hydrazine gave 58.⁴⁸ This reaction, however, fails to give *N*-substituted 58 with substituted hydrazines.^{48a}



As compared to the 2,3-benzodiazepines the 1,2-benzodiazepines have been very neglected. Only compounds 59⁴⁹ and 60⁵⁰ have been prepared. In addition the cyclopentane analog of 60 has been prepared from 61.⁵⁰



⁴⁴ N. P. Buu-Hoi, *Compt. Rend.* **209**, 321 (1939).

⁴⁵ A. Lieck, *Ber. Deut. Chem. Ges.* **38**, 3853 (1905).

⁴⁶ H. Wolbling, *Ber. Deut. Chem. Ges.* **38**, 3845 (1905).

⁴⁷ J. Gottlieb, *Ber. Deut. Chem. Ges.* **32**, 966 (1899).

⁴⁸ W. F. Whitmore and R. C. Cooney, *J. Am. Chem. Soc.* **66**, 1237 (1944).

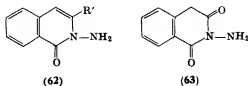
^{48a} G. Rosen and F. D. Popp, unpublished results, 1966.

⁴⁹ E. Fischer and H. Kuzel, *Ann. Chem.* **221**, 294 (1883).

⁵⁰ N. S. Gill, K. B. James, F. Lions, and K. T. Potts, *J. Am. Chem. Soc.* **74**, 4923 (1952).

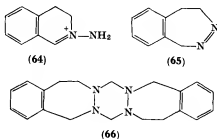
2. Reactions

On heating in acid a number of these diazepines undergo ring contraction to quinoline derivatives, **54** ($R=H$) giving **62**^{45, 46} and **58** ($R=H$) giving **63**.⁴⁸ Similarly **60** and its cyclopentanone analog with dry hydrogen chloride gave 2-phenyl-5,6,7,8-tetrahydroquinoline and 2-phenyl-5,6-cyclopentenopyridine, respectively.⁵⁰ Treatment of **53** ($R=CH_3$, $R'=C_6H_5$) with acid gave 1-methyl-2-(phenylamino)-3(2*H*)isoquinolone while base gave *o*-acetylphenylacetic acid hydrazone.⁴³



The nitro group in **58** ($R=NO_2$) was reduced with Raney nickel in ammonium hydroxide to the corresponding amine (**58**, $R=NH_2$).⁴⁸ Treatment of **54** ($R=H$, $R'=C_6H_5$) with methyl iodide in sodium hydroxide gave the *N*-methyl derivative.⁴⁶

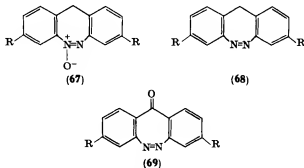
With phenyl isocyanate **48** yields the 3-anilinoformyl derivative while with sulfuric acid followed by sodium hydroxide it is converted via **64** into **49**.³⁹ Although **48** is catalytically reduced to **47** it is recovered unchanged from treatment with sodium in ethanol or lithium aluminum hydride. Treatment of **47** with hydrogen peroxide and sodium hydroxide gave a dihydrodiazepine believed to be **65** which is isomerized to **48** with acid. Finally, condensation of **47** with formaldehyde gave rise to **66**.³⁹



C. DIBENZO COMPOUNDS

1. *Synthesis*

Although 3,8-diamino-11*H*-dibenzo(*c,f*)-1,2-diazepine-5-oxide [67, R = NH₂, and 67, R = N(CH₃)₂] were first prepared in 1906^{51, 52} by reduction of 2,2'-dinitro-4,4'-diaminodiphenylmethane with zinc dust and ammonium chloride and subsequent air oxidation in basic medium, the ring system has not received any attention until recent years. The dibenzo compounds (67, R = Cl, Br, and I) were first prepared by the same method.⁵³ The parent diazepine (68, R = H)⁵⁴ and the dihalodiazepines (68, R = F, Cl, Br, and I)⁵⁵ have been prepared by lithium aluminium hydride reduction of the appropriate 2,2'-dinitrodiphenylmethane. In the case of the reduction of 2,2'-dinitro-4,4'-diiododiphenylmethane, either 68 (R = H) or 68 (R = I) could be obtained depending upon the amount of reducing agent used. Attempts to prepare the system 68 by oxidation of 2,2'-diaminodiphenylmethanes led to inconclusive results.⁵⁶



The synthesis of the dibenzodiazepinone (69, R = H) has been reported by action of alkaline glucose on 2,2'-dinitrobenzophenone.⁵⁶ This method, however, failed when applied to the 2,2'-dinitro-4,4'-dihalobenzophenones.⁵³ Treatment of the benzophenones with lithium aluminum hydride failed to yield any 69,^{53, 56} the products being those of carbon fission and reduction with hydrogenolysis.

⁵¹ H. Duval, *Compt. Rend.* **141**, 198 (1905).

⁵² H. Duval, *Bull. Soc. Chim. France* [4], **7**, 532 (1910).

⁵³ A. Catala and F. D. Popp, *J. Heterocyclic Chem.* **1**, 178 (1964).

⁵⁴ W. Theilacker and O. Korndorfer, *Tetrahedron Letters* p. 5 (1959).

⁵⁵ A. Catala and F. D. Popp, unpublished results, 1964.

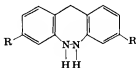
⁵⁶ R. B. Johns and K. R. Markham, *J. Chem. Soc.* p. 3712 (1962).

2. Reactions

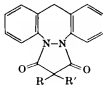
The amino group in **67** ($R = \text{NH}_2$) behaves in a normal manner and has been converted through the diazonium salt to **67** ($R = \text{H}$)^{57, 58} and **67** ($R = \text{NO}_2$).⁵⁵

The diazepine-*N*-oxide (**67**, $R = \text{H}$) has been reduced with sodium sulfide or with lithium aluminum hydride to **68** ($R = \text{H}$)^{57, 58} while **67** ($R = \text{NH}_2$) has been converted to **68** ($R = \text{NH}_2$) by zinc dust and base.^{51, 52} Use of these methods with the dihalo compounds (**67**; $R = \text{halogens}$) gave at best traces of the desired products.⁵³ The method of choice of preparation of **68** appears to be direct ring closure as mentioned in Section II, C, 1 rather than from the reduction of **67**.

Reduction of **68** with zinc dust and ammonia⁵⁴ or, better, hydrazine and Raney nickel^{53, 57, 58} gave rise to the dihydro compounds (**70**). For the most part these dihydro compounds are easily oxidized but they can be converted into stable adducts such as **71**.^{53, 59-61} More strenuous treatment of **68** ($R = \text{Br}$ or I) with hydrazine and Raney nickel gave rise to 2,2'-diaminodiphenylmethane.⁵³ The same compound is obtained from catalytic reduction of **70** ($R = \text{H}$).⁵⁸



(70)



(71)

Oxidation of **70** ($R = \text{H}$) with mercuric oxide converts it into the parent diazepine (**68**, $R = \text{H}$).⁵⁷ Oxidation of **68** with peracetic acid gave good yields of **67** and is a more convenient route to **67**⁵³ than the ring closure method mentioned in Section II, C, 1. Oxidation of **68** with chromic anhydride in glacial acetic acid gave rise to the diazepinone (**69**)⁵³ and appears to be a more convenient way of preparing **69** than the ring closure route. The chemistry of **69** has been

⁵⁷ N. L. Allinger and G. A. Youngdale, *Tetrahedron Letters* p. 10 (1959).

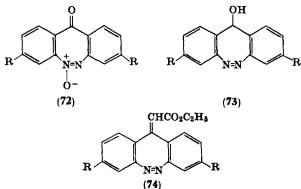
⁵⁸ N. L. Allinger and G. A. Youngdale, *J. Am. Chem. Soc.* **84**, 1020 (1962).

⁵⁹ J. R. Geigy A. G., British Patent 940,165 (1963); *Chem. Abstr.* **61**, 1816 (1964).

⁶⁰ H. S. Lowrie, *J. Med. Pharm. Chem.* **5**, 1362 (1962).

⁶¹ H. S. Lowrie, U.S. Patent 3,170,929 (1965); *Chem. Abstr.* **62**, 14706 (1965).

discussed from the aspect of a diazatropone.⁵⁶ Oxidation of **69** with peracetic acid gave rise to **72**.^{53, 62} With aluminum isopropoxide **69** gave **73** and with triethylphosphonoacetate in base **69** gave **74**.⁵⁵ Reaction of **72** with these same reagents gave the *N*-oxides of **73** and **74**.⁶² Although **69** fails to react with normal ketone reagents, **72** gave an oxime.⁶² Reaction of **69** ($R=H$) with sodium acetylides has been reported.^{62a} Ketenes have been found to add to the azo linkage in **69** ($R=H$) and **69** has been converted to the 11-keto analog of **71** ($R=R^1=H$).^{62a}



The ring contraction of **68** ($R=NH_2$) to an acridine has been reported.⁶³ The dibenzodiazepine system **68** appears to give a complex with a number of metal salts.^{63a}

D. OTHER 1,2-DIAZEPINES

Reaction of 1,5-dibromopentane with 4-phenyl- and 4-butyl-urazole has given rise to the novel 1,2-diazepine system (**75**).⁶⁴

The preparation of the naphthol(1,8-*d,e*)(1,2)diazepine system (**76**) has led to some confusion. Reaction of naphthoic anhydride and

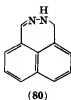
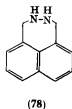
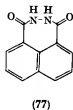
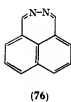
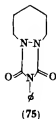
⁶² A. Catala, R. Dubois, and F. D. Popp, unpublished results, 1964-1965.

^{62a} W. Ried and S. Piesch, *Chem. Ber.* **99**, 233 (1966).

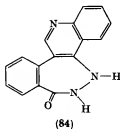
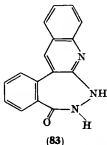
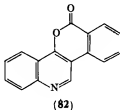
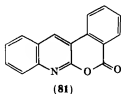
⁶³ H. Duval, *Compt. Rend.* **142**, 341 (1906).

^{63a} R. J. Dubois, J. Hagymassy, A. C. Noble, and F. D. Popp, *J. Heterocyclic Chem.*, in press.

⁶⁴ G. Zinner and W. Deucker, *Arch. Pharm.* **296**, 13 (1963).



hydrazine under certain conditions has been reported to yield **77**^{65, 66} but this work does not appear to be reproducible.^{65, 67} The system **76** can be obtained, however, by reaction of 1,8-bis(bromoethyl)naphthalene with the dipotassium salt of *tert*-butylhydrazodiformate



⁶⁵ A. Bistrzyki and J. Risi, *Helv. Chim. Acta* **8**, 810 (1925).

⁶⁶ E. S. Vasserman and G. P. Miklukhim, *J. Gen. Chem. (U.S.S.R.)* **10**, 202 (1940); *Chem. Abstr.* **34**, 7179 (1940).

⁶⁷ L. A. Carpino, *J. Am. Chem. Soc.* **85**, 2144 (1963).

followed by hydrogen chloride cleavage of the carbo-*tert*-butoxy group to yield the hydrochloric salt of **78**.⁶⁷ The free base (**78**) was somewhat unstable but could be oxidized with mercuric oxide to **79**. A number of other oxidizing agents led to an isomer of **79** believed to be **80**⁶⁷ which could also be obtained from **79** with hydrochloric acid.

The lactones **81** and **82** on heating with hydrazine hydrate gave rise to the diazepinones **83** and **84**, respectively.⁶⁸ Treatment of **83** and **84** with glacial acetic acid and sodium nitrite caused loss of a nitrogen atom with formation of a lactam.⁶⁸ This loss of a nitrogen has been noted above for other 1,2-diazepines and appears to be a fairly general reaction under a variety of conditions. A somewhat more complex quinobenzodiazepine has also been prepared.⁶⁹

III. 1,3-Diazepines

A. SIMPLE MONOCYCLIC COMPOUNDS

1. *Synthesis*

The diazepine **85** (tetramethyleneurea) has been prepared by a variety of routes. Among these are the treatment of tetramethylene diisocyanate with water,⁷⁰⁻⁷² the rearrangement of the oxime (**86**) in polyphosphoric acid,^{73, 74} and the reaction of 1,4-diaminobutane with sulfur, methanol, and carbon monoxide at high pressure.⁷⁵ A novel preparation of **85** involves the reaction of 1,4-diaminobutane with **87** to give the silylated diamine (**88**). Reaction of **88** with phosgene and triethylamine yielded the bistrimethylsilyldiazepine (**89**) which was then hydrolyzed in aqueous ethanol to give **85**.⁷⁶

The *N*-phenyl derivative of **85** has been obtained by refluxing **90**

⁶⁸ H. Diesbach, J. Gross, and W. Tschannen, *Helv. Chim. Acta* **34**, 1050 (1951).

⁶⁹ A. Meyer and H. Drutel, *Compt. Rend.* **207**, 923 (1938).

⁷⁰ Y. Iwakura, *Chem. High Polymers (Tokyo)* **4**, 94 (1947); *Chem. Abstr.* **45**, 2711 (1951).

⁷¹ Y. Iwakura, K. Uno, and K. Hamatani, *Nippon Kagaku Zasshi* **78**, 1416 (1957); *Chem. Abstr.* **54**, 1539 (1960).

⁷² S. Ozaki, T. Makaiyama, and K. Uno, *J. Am. Chem. Soc.* **79**, 4358 (1957).

⁷³ H. Behringer and H. Meier, *Ann. Chem.* **607**, 67 (1957).

⁷⁴ H. Behringer and H. Meier, *Ann. Chem.* **607**, 73 (1957).

⁷⁵ F. Applegath and R. A. Franz, U.S. Patent 2,874,149 (1959); *Chem. Abstr.* **53**, 12187 (1959).

⁷⁶ L. Birkofer, H. P. Kuhlthau, and A. Ritter, *Chem. Ber.* **93**, 2810 (1960).



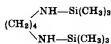
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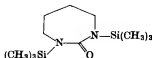
(86)



(87)



(88)



(89)

with aniline.⁷⁷ The reaction of succinyl chloride with *N,N'*-disubstituted ureas has been reported⁷⁸ to give the diazepine (91).

The thiourea (92) corresponding to 85 has also been prepared by several routes. Reaction of disodium tetramethylene bisdithiocarbamate (93) and ϵ -aminocaproic acid gave, in addition to an 81%



(90)



(91)

yield of *N,N'*-di-(ϵ -carboxypentylthiocarbamyl)tetramethylenediamine, and 18% yield of 92.⁷⁹ The diazepine (92) was also prepared from dithiocarbamide acid at 100°⁸⁰ and from the reaction of 1,4-diaminobutane and carbon disulfide.⁸¹



(92)



(93)

⁷⁷ R. Delaby and R. Damiens, *Festschr. Arthur Stoll* p. 474 (1957); *Chem. Abstr.* **53**, 376 (1959).

⁷⁸ G. Losse, E. Wottgen, and H. Just, *J. Prakt. Chem.* [4], **7**, 28 (1958).

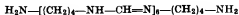
⁷⁹ A. F. McKay, S. Gelblum, E. J. Tarlton, P. R. Steyermark, and M. A. Mosley, *J. Am. Chem. Soc.* **80**, 3335 (1958).

⁸⁰ E. Strack, *Z. Physiol. Chem.* **180**, 198 (1929).

⁸¹ L. H. Conover, A. R. English, and C. E. Larrabee, U.S. Patent 2,921,073 (1960); *Chem. Abstr.* **54**, 8861 (1960).

A number of 1,3-diazepines of the type **94** have been prepared by reaction of 1,4-diaminobutane with the appropriate reagent.⁸²⁻⁹² The parent compound (**94**, R = H) has been obtained as a by-product in the thermal polymerization of the oligoamidines (**95**).⁹³

In addition to simple salt formation, treatment of nitro-L-arginine with base gave a 34% yield of the diazepine (**96**).⁹⁴ This same diazepine (**96**) was also prepared from L-ornithine and 2-methyl-1-nitro-2-thiopseudourea.⁹⁴

**(94)****(95)****(96)**

The bishydrazine (**97**) with benzaldehyde gave rise to diazepine **98**.⁹⁵ Reaction of tetramethylenediamine and half a mole of cyanogen yielded the bisdiazepine (**99**).⁹⁶

⁸² J. F. Arens, U.S. Patent 2,813,862 (1957); *Chem. Abstr.* **52**, 8212 (1958).

⁸³ J. A. Faust, A. Mori, and M. Sahyun, *J. Am. Chem. Soc.* **81**, 2214 (1959).

⁸⁴ T. Haga and R. Majima, *Ber. Deut. Chem. Ges.* **36**, 333 (1903).

⁸⁵ L. S. Hafner and R. Evans, *J. Org. Chem.* **24**, 1157 (1959).

⁸⁶ R. N. Johnson and H. M. Woodburn, *J. Org. Chem.* **27**, 3958 (1962).

⁸⁷ A. F. McKay and H. P. Thomas, *Can. J. Chem.* **29**, 391 (1951).

⁸⁸ A. F. McKay and G. F. Wright, *J. Am. Chem. Soc.* **70**, 430 (1948).

⁸⁹ P. Oxley and W. F. Short, *J. Chem. Soc.* p. 497 (1947).

⁹⁰ P. Oxley and W. F. Short, *J. Chem. Soc.* p. 859 (1950).

⁹¹ W. F. Short and P. Oxley, British Patent 593,659 (1947); *Chem. Abstr.* **42**, 1971 (1948).

⁹² W. F. Short and P. Oxley, British Patent 612,693 (1948); *Chem. Abstr.* **43**, 6670 (1949).

⁹³ C. Grundmann and J. Kreutzberger, *J. Polymer Sci.* **38**, 425 (1959).

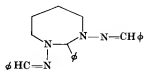
⁹⁴ R. Paul, G. W. Anderson, and F. M. Callahan, *J. Org. Chem.* **26**, 3347 (1961).

⁹⁵ H. V. Daenicker and J. Druey, *Helv. Chim. Acta* **40**, 918 (1957).

⁹⁶ K. Matsuda, U.S. Patent 2,819,262 (1958); *Chem. Abstr.* **52**, 9230 (1958).



(97)



(98)



(99)

When 3-quinuclidinone (**100**) was treated with sodium azide and sulfuric acid⁹⁷ or its oxime was treated with oleum⁹⁸ a mixture of the 1,3- and 1,4-diazepines (**101** and **102**) was obtained. The compounds can be considered as bridged diazepines. More recent work, however, has shown structure **101** to be incorrect.^{98a}



(100)



(101)



(102)

2. Reactions

Hydrolysis of diazepine **85** gave rise to 1,4-diaminobutane^{71, 72} while treatment of **85** with phosphorus pentasulfide gave **92**.⁷⁴ The infrared spectrum of **85** has been studied.^{99, 100} In studies carried out on the molten monomer, **92** polymerized but **85** did not.¹⁰¹ Condensation of **92** with formaldehyde gave the bis compound (**103**) but no

⁹⁷ E. E. Mikhlin and M. V. Rubtsov, *Zh. Obshch. Khim.* **33**, 2167 (1963).

⁹⁸ M. V. Rubtsov, E. E. Mikhlin, V. Y. Vorobeva, and A. D. Yanina, *Zh. Obshch. Khim.* **34**, 2222 (1964).

^{98a} E. E. Mikhlin, V. Y. Vorobeva, V. I. Shedchenko, and M. V. Rubtsov, *Zh. Org. Khim.* **1**, 1336 (1965).

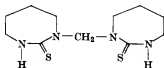
⁹⁹ H. K. Hall, Jr. and R. Zbinden, *J. Am. Chem. Soc.* **80**, 6428 (1958).

¹⁰⁰ R. Mecke, Jr. and R. Mecke, *Chem. Ber.* **89**, 343 (1956).

¹⁰¹ H. K. Hall, Jr. and A. K. Schneider, *J. Am. Chem. Soc.* **80**, 6409 (1958).

higher derivatives.¹⁰² Reaction of 2-bromopyridine-*N*-oxide hydrobromide with **92** in acetone gave compound **104**.⁸¹

Treatment of **94** ($R = -NHNO_2$) with ammonia gave rise to the 2-imino-1,3-diazepine derivative¹⁰³ while nitration gave the *N,N'*-dinitro derivative of **85**.¹⁰⁴ In studies with **94** ($R = -NHNO_2$) it has



(103)



(104)

been stated⁸⁸ that no tautomeric forms have yet been detected. The diazepine (**94**, $R = CH_2OH$) has been treated with thionyl chloride to give **94** ($R = CH_2Cl$) which reacts with carboxylic acids to give **94** ($R = CH_2CO_2R'$).⁸³

Hydrogenation of **96** over palladium on carbon gave the corresponding imino compound with loss of the nitro group.⁹⁴



(105)



(106)



(107)

A bicyclic derivative (**105**) of a 1,3-diazepine was prepared by treating **94** [$R = NH(CH_2)_2OH$] with thionyl chloride and then potassium hydroxide.¹⁰⁵ Nitration of **105** gave the nitrate salt of **106**.¹⁰⁵ The reaction of **94** ($R = SR^1$) with isothiocyanates has been studied.^{105a}

Reduction of **101** with lithium aluminum hydride gave the diamine (**107**) which formed *N*-methyl and monoacyl derivatives.⁹⁷

¹⁰² H. Staudinger and G. Niessen, *Makromol. Chem.* **15**, 75 (1955).

¹⁰³ D. Stefanye and W. L. Howard, *J. Am. Chem. Soc.* **77**, 761 (1955).

¹⁰⁴ A. F. McKay and G. F. Wright, *J. Am. Chem. Soc.* **70**, 3990 (1948).

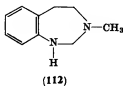
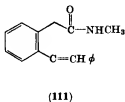
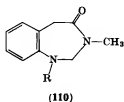
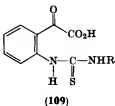
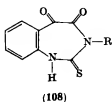
¹⁰⁵ A. F. McKay and M. E. Kreling, *Can. J. Chem.* **35**, 1438 (1957).

^{105a} F. D'Angeli, C. DiBello, and V. Giormani, *Gazz. Chim. Ital.* **95**, 735 (1965).

B. BENZO COMPOUNDS

Relatively little work has been carried out on 1,3-diazepines with a benzene ring fused to the diazepine system.

A few derivatives of the 1*H*-1,3-benzodiazepine system have been prepared. Ghosh¹⁰⁶ has reported the synthesis of **108** (R = phenyl or *p*-tolyl) by treatment of **109** with acetic anhydride. No evidence for structure **108** has been presented other than its stability in hot concentrated hydrochloric acid. It is soluble in cold dilute alkali and is precipitated unchanged by acids. DeStevens has summarized¹⁰⁷ the work of his group^{108, 109} on some 1*H*-1,3-benzodiazepine derivatives. Condensation of 2-(*o*-aminophenyl)-*N*-methylacetamide with formaldehyde in neutral solvents such as diethylene glycol dimethyl ester at 95° gave **110** (R = H) while use of benzaldehyde under these conditions gave only the azomethine (**111**). These results were confirmed by condensation of the sodium borohydride reduction product of **111** with formaldehyde to yield **110** (R = benzyl). Hydrogenolysis of the benzyl group gave a substance identical with that obtained from the original acetamide and formaldehyde. Lithium aluminum hydride reduction of **110** (R = H) or lithium aluminum



¹⁰⁶ T. N. Ghosh, *J. Indian Chem. Soc.* **10**, 583 (1933).

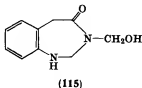
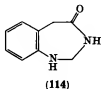
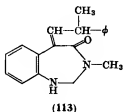
¹⁰⁷ G. deStevens, *Record Chem. Progr. (Kreage-Hooker Sci. Lib.)* **23**, 105 (1962).

¹⁰⁸ G. deStevens and M. Dughi, *J. Am. Chem. Soc.* **83**, 3087 (1961).

¹⁰⁹ G. deStevens, M. Dughi, H. Lukaszewski, and H. Blatter, *Oesterr. Chemiker-Ztg.* **63**, 177 (1962); *Chem. Abstr.* **59**, 11479 (1963).

hydride reduction of **110** ($R = \text{benzyl}$) followed by hydrogenolysis gave rise to 2,3,4,5-tetrahydro-3-methyl-1*H*-1,3-benzodiazepine (**112**). The corresponding 3-ethyl, propyl, and benzyl analogs also were prepared.

Condensation of α -phenylpropionaldehyde with 2-(*o*-aminophenyl)-*N*-methylacetamide took place on carbon to give the diazepine (**113**) after treatment with formaldehyde. Attempts to condense this amide with formic acid, formamide, acetic anhydride, or ethyl orthoformate did not give any diazepine, but rather gave oxindole or oxindole derivatives. Use of the unsubstituted amide of *o*-aminophenylacetic acid and formaldehyde led to variable results¹⁰⁷ with **114** and **115** being obtained. The position of the hydroxymethyl group in **115** was demonstrated by a sequence through the unmethylated analog of **111**.

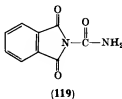
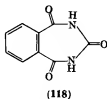
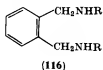


The tetrahydrodiazepine (**112**) was found¹⁰⁷ to be a highly unstable substance. On the other hand, the 4-keto derivative (**110**, $R = H$) was quite stable, although refluxing a dilute aqueous hydrochloric acid solution led to the formation of what was believed to be an oxindole polymer. This ready acid hydrolysis was attributed to the essentially acetal-like character of the grouping $N-CH_2-N$. The low basicity of **110** ($R = H$) ($pK_a < 2$) is of interest since *N*-methyl-*o*-toluidine has a pK_a of 4.87. The inductive effect plus the mesomeric influence of the amide carbonyl and internal strain effects resulting in a certain amount of bond opposition appear to explain this basicity.¹⁰⁷

The reaction of equimolar quantities of sodium phenylacetylide and

phenyl isocyanate gives a small amount of material tentatively formulated as a benzo-1,3-diazepine.^{109a}

Even less attention has been directed to the 1*H*-2,4-benzodiazepine system. Condensation of formaldehyde with the diamines (**116**, R = phenyl and *p*-tolyl) has been reported¹¹⁰ to lead to diazepines (**117**). Phthaloylurea and its derivatives had been assigned structure **118**¹¹¹ but X-ray analysis¹¹² and chemical methods¹¹³ have shown that phthaloylurea is best represented by formula **119**.



A number of derivatives of the pyrido(1,2-*a*)-1,3-diazepine system (**120**) were prepared by condensation of α -aminopyridine with anhydrides of tetraalkylsuccinic acids.¹¹⁴ Thus, compounds of the type **120** were prepared. Use of 2,6-diaminopyridine led to the 7-amino analog of **120** (R = R' = C₂H₅). 2-Oxo-2,3,4,5-tetrahydro-1*H*-pyrido(1,2-*a*)-1,3-diazepinium bromide (**121**) was synthesized¹¹⁵ by treatment of 2-aminopyridine with γ -bromobutyryl bromide, the crude bromoamide (**122**) being cyclized in chloroform. The diazepine (**121**) was hydrolyzed with ethanolic hydrobromic acid to give the 2-aminopyridinium ester (**123**). This work was carried out to compare **121** with a product obtained from the Beckmann rearrangement of **124**.¹¹⁶ They were not identical.

^{109a} C. W. Bird, *J. Chem. Soc.* p. 5762 (1965).

¹¹⁰ M. Scholtz and K. Jaross, *Ber. Deut. Chem. Ges.* **34**, 1504 (1901).

¹¹¹ C. S. Smith and C. J. Cavallito, *J. Am. Chem. Soc.* **61**, 2218 (1939).

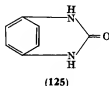
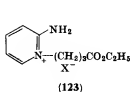
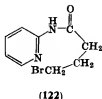
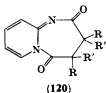
¹¹² D. Grdenic and A. Bezjak, *Arkiv Kemi* **25**, 101 (1953).

¹¹³ V. Hahn, P. Hammes, and Z. Geric, *Experientia* **10**, 11 (1954).

¹¹⁴ E. Ott and F. Hess, *Arch. Pharm.* **276**, 181 (1938).

¹¹⁵ A. Fozard and G. Jones, *J. Chem. Soc.* p. 2763 (1964).

¹¹⁶ A. R. Collicut and G. Jones, *J. Chem. Soc.* p. 4101 (1960).



The claimed formation of the ring system **125**, which can be considered as a diazepine, should be noted.¹¹⁷

C. DIBENZO COMPOUNDS

1. Synthesis

A wide variety of derivatives of 5*H*-dibenzo(*d,f*)-(1,3)-diazepine (**126**) have been prepared. In addition to the parent compound (**126**, R=H),^{118, 119} other derivatives substituted in the 6-position have been prepared to include alkyl,^{118, 120-126} aryl,^{119, 123-125, 127, 128}

¹¹⁷ P. C. Guha and H. K. Benerjee, *J. Indian Inst. Sci.* **11A**, 231 (1928).

¹¹⁸ Y. A. Levin, A. P. Mokhova, and V. A. Kukhtin, *Zh. Obshch. Khim.* **31**, 1573 (1961).

¹¹⁹ W. Ried and W. Storbeck, *Chem. Ber.* **95**, 459 (1962).

¹²⁰ A. E. Blood and C. R. Noller, *J. Org. Chem.* **22**, 873 (1957).

¹²¹ P. T. Charlton, G. M. Maliphant, P. Oxley, and D. A. Peak, *J. Chem. Soc.* p. 485 (1951).

¹²² H. Moehrke, H. Koch, and H. von Freyberg, German Patent 865,305 (1949); *Chem. Abstr.* **52**, 20201 (1958).

¹²³ W. Ried and E. Schmidt, *Ann. Chem.* **676**, 114 (1964).

¹²⁴ W. Ried and A. Sinharay, *Chem. Ber.* **97**, 1214 (1964).

^{124a} W. Ried and A. Sinharay, *Chem. Ber.* **98**, 3523 (1965).

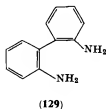
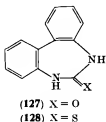
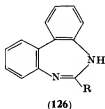
¹²⁵ S. Sako, *Mem. Coll. Eng. Kyushu Imp. Univ.* **6**, 263 (1932); *Chem. Abstr.* **26**, 3246 (1932).

¹²⁶ R. Weiss and L. Chledowski, *Monatsh. Chem.* **65**, 357 (1935).

¹²⁷ A. E. S. Fairfull, D. A. Peak, W. F. Short, and T. I. Watkins, *J. Chem. Soc.* p. 4700 (1952).

¹²⁸ A. E. S. Fairfull, V. Petrow, and W. F. Short, *J. Chem. Soc.* p. 3549 (1955).

alkoxy,¹¹⁹ methylmercapto,¹²⁹ amino,¹²⁹ hydroxy,^{119,130-133} and sulfhydryl^{129,132} compounds. The last two are generally written as the -one and -thione forms **127** and **128**, respectively. All of these dibenzodiazepines have been prepared from 2,2'-diaminodiphenyl (**129**) or from a derivative of **129**.



The parent compound (**126**, R = H) was first obtained by treating the *N,N'*-diformyl derivative of **129** with dry hydrogen chloride in boiling xylene.¹²⁵ It also was obtained, together with a dimer, from the mono-*N*-formyl derivative of **129**¹¹⁹ and from the reaction of **129** with ethyl orthoformate.^{118,119} Under some conditions this latter reaction also gave rise to 6-ethoxy-6,7-dihydrodibenzo(*d,f*)-1,3-diazepine which was converted to **126** (R = H) by reaction with additional ethyl orthoformate.¹¹⁹ Other ortho esters have also been used to prepare analogs of **126**.^{118,119} The 6-methyl and 6-phenyl compounds (**126**, R = CH₃ and C₆H₅) also have been prepared by heating the corresponding monoacyl derivatives of **129** with phosphorus trichloride. In this manner use of levo- or dextrorotatory **130** gave optically active diazepines.¹²⁵ The absolute configuration of these diazepines has been studied.^{134,135} Treatment of 2,2'-dibenzamidobiphenyl with phosphorus oxychloride gave, in addition to **126** (R = C₆H₅), 5-benzamido-9-phenylphenanthridine.¹²⁸ Aryl¹²⁷

¹²⁹ W. E. Kreighbaum and H. C. Scarborough, *J. Med. Pharm. Chem.* **7**, 310 (1964).

¹³⁰ R. A. Labriola, *J. Org. Chem.* **5**, 329 (1940).

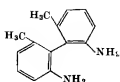
¹³¹ R. A. Labriola and A. Felite, *Anales Asoc. Quim. Arg.* **32**, 57 (1944); *Chem. Abstr.* **39**, 1405 (1945).

¹³² R. J. W. LeFevre, *J. Chem. Soc.* p. 733 (1929).

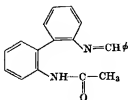
¹³³ S. von Niementowski, *Ber. Deut. Chem. Ges.* **34**, 3325 (1901).

¹³⁴ D. D. Fitts, M. Siegel, and K. Mislow, *J. Am. Chem. Soc.* **80**, 480 (1958).

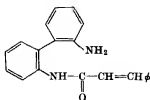
¹³⁵ F. A. McGinn, A. K. Lazarus, M. Siegel, J. E. Ricci, and K. Mislow, *J. Am. Chem. Soc.* **80**, 476 (1958).



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(131)



(132)

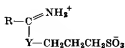
and alkyl¹²¹ derivatives of I are also obtained from the benzene-sulfonate of **129** and the appropriate nitrile.

Treatment of **131** with phosphorus oxychloride gave **126** ($R = CH=CH-C_6H_5$), presumably via an inter- or intramolecular aldol-type condensation followed by elimination to give an intermediate of type **132** which cyclizes.¹²⁰ The same diazepine also has been obtained from **132**.¹²⁰

Recent work has made use of the reaction of compounds of the types **133**^{124, 124a} and **134** ($Y = S$ or O)¹²³ with **129** to give **126**. The 6-amino compound (**126**, $R = NH_2$) has been prepared by fusion of **129** and *S*-methylisothiurea sulfate,¹²⁹ while fusion of **129** and carbodiimides gave rise to compounds of the type **126** ($R = NHR'$).¹²⁹ The bis diazepine **126** ($R = \text{another dibenzodiazepine unit}$) has been prepared.^{135a}



(133)



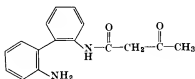
(134)

The urea (**127**) has been obtained from **129** and urea¹²³ or carbamide¹³² or acetoacetic ester¹¹⁹ while **128** has been prepared from **129** and carbon disulfide.^{129, 132} The reaction with acetoacetic ester is believed to pass through **135** and **136**, and under certain conditions

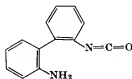
^{135a} W. Ried and A. Sinharay, *Chem. Ber.* **98**, 3532 (1965).

135 can be isolated with **127**. The diazide (**137**) also has been converted into **127**.^{130, 131}

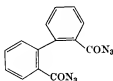
The 6,7-dihydrodiazepine [**138**, R = CH(OEt)₂] has been obtained from **129** and glyoxal monoacetal.¹³⁶ Use of chloral gave **138**



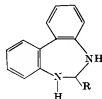
(135)



(136)



(137)



(138)

(R = CCl₃).¹²⁶ That this compound was **138** and not a mono-Schiff base of chloral and **129** was demonstrated by its conversion into a dinitro derivative.

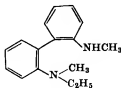
2. Reactions

Relatively little has been reported on the reactions of dibenzo-(*d,f*)-1,3-diazepines. Attempts to methylate **126** (R = CH₃ or aryl) with methyl iodide or methyl sulfate have failed,^{118, 125, 127} and the products obtained are a result of cleavage of the heterocycle. For example, **139** is obtained from the reaction of methyl iodide with **126** (R = CH₃)¹²⁵ and **140** is obtained from **126** (R = *p*-O₂NC₆H₄) and methyl sulfate.¹²⁷ Methylation, however, of the sodium salt in liquid ammonia with methyl iodide gave the tertiary base **141**.¹¹⁸ It is of interest to note that solutions of both **141** and the sodium salt of **126** (R = CH₃) in liquid ammonia are intensely red,¹¹⁸ as is the sodium salt of **126** (R = CH=CHC₆H₅).¹²⁰ The *N*-methyl compound (**141**) gave a quaternary salt by treatment with methyl sulfate in boiling benzene.

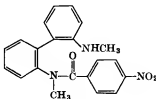
In addition to the ring openings reported during methylation, at

¹³⁶ N. Vinot, *Compt. Rend.* **253**, 2986 (1961).

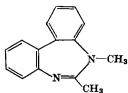
least two other reports of the opening of the heterocyclic ring have appeared. Catalytic reduction of **126** ($R = CH=CHC_6H_5$) presumably led to ring opening, although the product was not studied.¹²⁰ This same diazepine is hydrolyzed to 2-amino-2'-cinnamidobiphenyl with silver and sodium carbonate. Glacial acetic acid hydrolyzes diazepine **142** to a monobenzyldiaminodinitrobiphenyl.¹²⁷



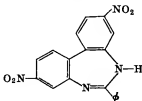
(139)



(140)



(141)



(142)

The diazepinone (**127**) reacted with benzoyl chloride to give the *N,N'*-dibenzoyl derivative¹³⁷ and was brominated in acetic acid at 20°. ¹³⁸ Compounds **127** and **128** undergo the bis-semidine inversion when heated with 3% hydrochloric acid.¹¹⁷ The thione (**128**) is converted in high yield into the methylmercapto diazepine (**126**, $R = SCH_3$) by reaction with methyl iodide in tetrahydrofuran.¹²⁹ The thione does not react with amines, but the 6-methylmercapto compound on heating with amines or amine hydrochlorides gave rise to the 6-amino compounds (**126**, $R = NR'R''$).¹²⁹ A number of these amino derivatives have exhibited some medicinal activity. With *n*-butanol the 6-methylmercapto compound is quantitatively converted into **127**.¹²⁹

Infrared and ultraviolet evidence¹³⁹ confirms the structure **127** and

¹³⁷ O. Christmann, *Chem. Ber.* **98**, 1282 (1965).

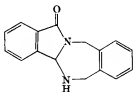
¹³⁸ M. Murakami and I. Moritani, *J. Chem. Soc. Japan, Pure Chem. Sect.* **70**, 236 (1949).

¹³⁹ R. B. Lund, Ph.D. Dissertation, University of Washington, Seattle, Washington, 1959.

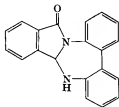
excludes the possibility of enol tautomerism as well as the possibility of carbonyl polarization.

D. OTHER 1,3-DIAZEPINES

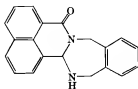
In addition to compounds related to **126** which have been prepared from 2,2'-diamino-1,1'-dinaphthyl,¹²² 2',3-diamino-2,3'-dipyridine,¹⁴⁰ 2,7-dimethyl-4,5-diamino-*p*-phenanthroline,¹⁴¹ and α -imino- β -(*o*-acetamidophenyl)- γ -butyrolactone,^{142, 143} a number of other 1,3-



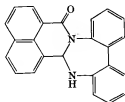
(143)



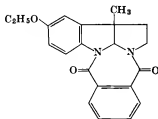
(144)



(145)



(146)



(147)

¹⁴⁰ W. Brydowna, *Roczniki Chem.* **14**, 304 (1934).

¹⁴¹ G. Jacini, *Gazz. Chim. Ital.* **70**, 621 (1940).

¹⁴² H. Plieninger, *Angew. Chem.* **67**, 400 (1955).

¹⁴³ H. Plieninger and I. Nogradi, *Chem. Ber.* **88**, 1965 (1955).

diazepines such as **143**,^{144, 145} **144**,¹⁴⁵ **145**,¹⁴⁵ **146**,¹⁴⁵ **147**,¹⁴⁶ and others^{146a} have been prepared.

IV. 1,4-Diazepines

A. SIMPLE MONOCYCLIC COMPOUNDS

1. *Synthesis*

The completely saturated 1,4-diazepine (homopiperazine) (**148**, $R=R'=H$) has been prepared by several methods. Reaction of 1,3-dibromopropane with the benzenesulfonamide¹⁴⁷ or the *p*-toluenesulfonamide¹⁴⁸ of ethylenediamine gave the sulfonamide of **148** which could be readily hydrolyzed by acid to the parent compound (**148**, $R=R'=H$). Reaction of 1,3-dibromopropane and *N,N,N',N'*-tetramethylethylenediamine gave the dimethobromide of **148** ($R=R'=CH_3$) which was readily demethobrominated to **148** ($R=R'=CH_3$).¹⁴⁹ Homopiperazine is also prepared when **149** ($R=H$) is treated with Raney nickel in tetralin.¹⁵⁰ This same method has been used with **149** ($R=CH_3$, C_2H_5 , and CH_3CO) to synthesize a variety of monosubstituted homopiperazines (**148**, $R=H$).¹⁵¹ Homopiperazine and its 1-, 2-, 5-, and 6-monomethyl derivatives have been prepared via reductive cyclization of *N*-(2-cyanoethyl)ethylenediamine and its methyl derivatives.¹⁵² Dehydrative cyclization of **150** ($R=H$) also gave homopiperazine.¹⁵³ This method has been extended to *C*-methyl^{149, 154} but not to *N*-methyl homopiperazines,¹⁵⁵ although **150** ($R=CH_2CH_2OEt$) gave good yields of **148** ($R=CH_2CH_2OEt$, $R'=H$).^{149, 155}

¹⁴⁴ H. H. Hatt and E. M. F. Stevenson, *J. Chem. Soc.* p. 199 (1952).

¹⁴⁵ E. M. F. Stevenson, *J. Chem. Soc.* p. 5024 (1952).

¹⁴⁶ R. Robinson and H. Sugimoto, *J. Chem. Soc.* p. 304 (1932).

^{146a} J. R. Geigy A. G., Belgian Patent 659,530 (1965); *Chem. Abstr.* **64**, 6664 (1966).

¹⁴⁷ L. Bleier, *Ber. Deut. Chem. Ges.* **32**, 1826 (1899).

¹⁴⁸ C. C. Howard and W. Marckwald, *Ber. Deut. Chem. Ges.* **32**, 2038 (1899).

¹⁴⁹ S. M. McElvain and L. W. Bannister, *J. Am. Chem. Soc.* **76**, 1126 (1954).

¹⁵⁰ A. Kotelko, *Acta Polon. Pharm.* **18**, 171 (1961); *Chem. Abstr.* **56**, 7131 (1962).

¹⁵¹ A. Kotelko, *Acta Polon. Pharm.* **19**, 215 (1962); *Chem. Abstr.* **59**, 7370 (1963).

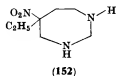
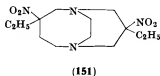
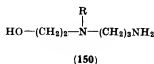
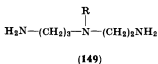
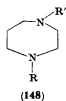
¹⁵² F. Poppelsdorf and R. C. Myerly, *J. Org. Chem.* **26**, 131 (1961).

¹⁵³ T. Ishiguro and M. Matsumura, *Yakugaku Zasshi* **78**, 153 (1959).

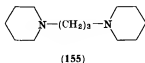
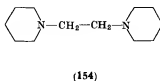
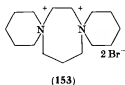
¹⁵⁴ T. Ishiguro and M. Matsumura, *Yakugaku Zasshi* **79**, 302 (1959).

¹⁵⁵ R. Kolinski and T. Urbanski, *Bull. Acad. Polon. Sci.* **3**, 493 (1955).

The reaction of 1-nitropropane, formaldehyde, and ethylenediamine gave **151** together with a small amount of **152**.¹⁵⁶ Compound **151** was also prepared by reaction of **152** with 2-nitro-2-ethylpropane-1,3-diol in the presence of base.^{156, 156}



Homopiperazinium salts (**153**) have been prepared by reaction of **154** with 1,3-dibromopropane^{157, 158} or **155** with 1,2-dibromoethane.¹⁵⁷ Similar reactions were also carried out using a variety of



other amines in place of one or both of the piperidines in **154** and **155**.^{157, 159}

The Schmidt and Beckmann reactions have been useful in the synthesis of homopiperazinones through ring expansion. In this

¹⁵⁶ T. Urbanski and R. Kolinski, *Roczniki Chem.* **30**, 201 (1956).

¹⁵⁷ J. V. Braun and O. Goll, *Ber. Deut. Chem. Ges.* **60**, 339 (1927).

¹⁵⁸ M. Scholtz, *Ber. Deut. Chem. Ges.* **35**, 3047 (1902).

¹⁵⁹ F. F. Blicke and E. B. Hotelling, *J. Am. Chem. Soc.* **76**, 2427 (1954).

manner, 4-piperidone with hydrazoic acid and sulfuric acid gave **156** ($R=H$)¹⁶⁰ and 1-methyl-4-piperidone gave **156** ($R=CH_3$).¹⁶⁰⁻¹⁶² Other 1-substituted 4-piperidones have also been used.^{163, 163a} The use of a symmetrical compound (**157**, $R=R^3=R^4=CH_3$ or $R=R^3=R^4=R^5=CH_3$)^{160, 164} does not present any problems; however, with an unsymmetrical compound two products are possible. In each of these cases, however, only one product has been isolated, although in most cases the authors do not preclude the possibility of another isomer in the crude product. In this manner **157** ($R=R^4=CH_3$; $R^2=R^5=CH_3$; $R^6=CH_3$, $R^2=CO_2Et$; $R^2=R^5=CH_3$, $R^6=CO_2Et$; and $R^5=CH_3$, $R^2=C_6H_5$) gave **158** ($R=R^4=CH_3$; $R^2=R^6=CH_3$; $R^5=CH_3$, $R^6=CO_2Et$; $R^2=R^5=CH_3$, $R^6=CO_2Et$; and $R^5=CH_3$, $R^2=C_6H_5$), respectively.^{163, 165, 166}



(156)



(157)



(158)

Beckmann rearrangement of 2,2,6,6-tetramethyl-4-piperidone oxime with thionyl chloride followed by oxidation gave the stable free radical **159**.¹⁶⁷ Beckmann rearrangement of the *N*-oxide radical of the piperidone oxime gave the same free radical (**159**).¹⁶⁸

The homopiperazinone (**160**) was isolated from a complex mixture arising from the reaction of ethylenediamine and methyl crotonate.¹⁶⁹

¹⁶⁰ S. C. Dickerman and H. G. Lindwall, *J. Org. Chem.* **14**, 530 (1949).

¹⁶¹ A. H. Sommers, R. J. Michaels, Jr., and A. W. Weston, *J. Am. Chem. Soc.* **76**, 5805 (1954).

¹⁶² P. S. Wadia and N. Anand, *J. Sci. Ind. Res. (India)* **17B**, 31 (1958).

¹⁶³ S. C. Dickerman and A. J. Besozzi, *J. Org. Chem.* **19**, 1855 (1954).

^{163a} A. B. Sen and K. Shanker, *J. Prakt. Chem.* [4] **29**, 312 (1965).

¹⁶⁴ J. E. Robertson, J. H. Biel, and F. DiPierro, *J. Med. Chem.* **6**, 381 (1963).

¹⁶⁵ S. C. Dickerman and E. J. Mariconi, *J. Org. Chem.* **20**, 206 (1955).

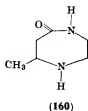
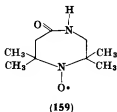
¹⁶⁶ K. Hohenlohe-Oehringen, *Monatsh. Chem.* **96**, 257 (1965).

¹⁶⁷ E. G. Rozantsev and R. A. Papko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 2254 (1962).

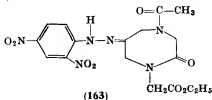
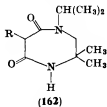
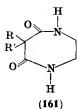
¹⁶⁸ E. G. Rozantsev and R. A. Papko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 764 (1963).

¹⁶⁹ W. M. Corbett and J. E. McKay, *J. Chem. Soc.* p. 2930 (1961).

The preparation of a number of 1,4-diazepines with two carbonyl functions has been reported. A variety of alkyl and dialkyl malonic esters have been reacted with ethylenediamine to give **161**.^{170, 171}



Although these could be considered as homodesoxybarbituric acids, they exhibited no practical pharmacological activity. Use of *N*-(2-aminoisobutyl)isopropylamine with alkyl malonic esters gave **162**¹⁷² which was shown to be monomeric. It has been reported that the



parent compound (**161**, $R = R' = H$) can be prepared by reaction of ethylenediamine with malonamide¹⁷³ or by the passage of C_3O_2 into an ethylenediamine solution.¹⁷⁴ The possibilities for tautomerism in **161** and **162** do not appear to have been studied.

¹⁷⁰ J. Buchi, A. Aebi, R. Bosshart, and E. Eichenberger, *Helv. Chim. Acta* **39**, 950 (1956).

¹⁷¹ A. W. Dox, *J. Am. Chem. Soc.* **55**, 3871 (1933).

¹⁷² I. J. Pachter and J. L. Riebsomer, *J. Org. Chem.* **15**, 909 (1950).

¹⁷³ M. Freund, *Ber. Deut. Chem. Ges.* **17**, 133 (1884).

¹⁷⁴ L. B. Dashkevich and V. M. Siraya, *Zh. Obshch. Khim.* **32**, 2330 (1962).

The mono-2,4-dinitrophenylhydrazone of a dicarbonyl 1,4-diazepine (**163**) has been prepared by treating the reaction product from the 2,4-dinitrophenylhydrazone of dichloroacetone and ethyl glycinate with acetic anhydride.¹⁷⁵



(164)



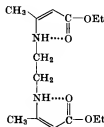
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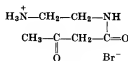
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(169)



(170)

Ethylenediamine has been condensed with a variety of compounds to produce 1,4-diazepine systems. For example, use of a β -diketone such as acetylacetone gave **164** or **165**.^{176, 177} Other β -diketones^{176, 178} behave in a similar manner. The reaction of malondialdehyde diacetal with N,N' -diphenylethylenediamine in the presence of perchloric acid also took a similar course to give **166**.¹⁷⁹ Substituted malon-

¹⁷⁵ M. Rink and K. Feiden, *Arch. Pharm.* **295**, 121 (1962).

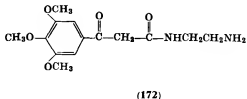
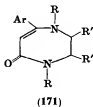
¹⁷⁶ M. A. Rosanov, *J. Russ. Phys. Chem. Soc.* **47**, 611 (1915).

¹⁷⁷ G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta* **23**, 1139 (1940).

¹⁷⁸ W. Ried and W. Hohne, *Chem. Ber.* **87**, 1811 (1954).

¹⁷⁹ B. Eistert and F. Haupter, *Chem. Ber.* **93**, 264 (1960).

dialdehydes gave rise to 6-substituted analogs of **166**.¹⁷⁶ Use of β -ketoesters has been reported¹⁷⁸ to give **167**; however, more recent work indicates that while with ethyl benzoylacetate a diazepine is obtained, with acetoacetic ester the bisenamine (**168**) is formed.¹⁸⁰ The latter diazepine, however, on the basis of ultraviolet, infrared, and NMR data appears to exist as the enamine tautomer (**169**, $R = C_6H_5$) rather than the ketimine (**167**). Although, as noted above,



it was not possible to prepare the methyl analog (**169**, $R = CH_3$) directly, it was prepared by reaction of the salt (**170**) with ammonia.¹⁸⁰ Two recent papers^{180a, 180b} should also be consulted.

The condensation of other β -ketoesters with ethylenediamine, 2,3-diaminobutane, and *N,N'*-dimethylethylenediamine gave compounds of the general structure **171** except in the case of ethyl 3,4,5-trimethoxybenzoyl acetate.¹⁸¹ In this latter case the desired compound [**169**, $R = 3,4,5-(CH_3O)_3C_6H_2$] was prepared by cyclization of **172**.¹⁸¹

Condensation of ethylenediamine with α,β -unsaturated carbonyl

¹⁸⁰ C. M. Hofmann and S. R. Safir, *J. Org. Chem.* **27**, 3565 (1962).

^{180a} C. Barnett, H. P. Cleghorn, G. E. Cross, D. Lloyd, and D. R. Marshall, *J. Chem. Soc., C., Org.* p. 93 (1966).

^{180b} D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc., C., Org.* p. 780 (1966).

¹⁸¹ C. M. Hofmann, G. E. Wiegand, and S. R. Safir, *J. Chem. Eng. Data* **10**, 188 (1965).

compounds has been reported in some cases to give the 1,4-diazepine system.¹⁸²⁻¹⁸⁵ For example, mesityl oxide gave **173**.^{182, 184} This reaction of α,β -unsaturated compounds, however, is not specific for the formation of a seven-membered ring.¹⁷⁸

A novel preparation of the 1,4-diazepine system (**174**) has been reported through isomerization of the Schiff base (**175**).^{186, 187} This same type of diazepine (**176**) was prepared by the reaction of acetylacetone and meso-1,2-diphenylethylenediamine.¹⁸⁸ Spectroscopic studies indicated that it was in the form shown. The NMR spectra of these 2,3-dihydro-1,4-diazepines and their cations have been discussed.¹⁸⁷ The Schiff base of benzaldehyde and 1,2,3-triaminocyclopropane also isomerizes to give **174** ($R = C_6H_5$, $R' = C_6H_5CH=N$).^{186, 187, 189} The mass spectrometric fragmentation of compounds of the type **176** has been reported.^{189a}

2. Reactions

A variety of derivatives of homopiperazine have been prepared^{161, 163a, 190-198} but these reactions require no special comment as

¹⁸² I. Guareschi, *Atti. Accad. Sci. Torino* **29**, 692 (1894).

¹⁸³ H. K. Hall, Jr., *J. Am. Chem. Soc.* **80**, 6406 (1958).

¹⁸⁴ L. K. Mushkalo and Z. I. Shokol, *Zh. Obshch. Khim.* **30**, 1023 (1960).

¹⁸⁵ W. Heinrich and W. Heigel, German Patent 1,047,785 (1958); *Chem. Abstr.* **55**, 4552 (1961).

¹⁸⁶ H. A. Staab and F. Vogl, *Tetrahedron Letters* p. 51 (1965).

¹⁸⁷ H. A. Staab and F. Vogl, *Chem. Ber.* **98**, 2701 (1965).

¹⁸⁸ H. A. Staab and F. Vogl, *Chem. Ber.* **98**, 2681 (1965).

¹⁸⁹ H. A. Staab and F. Vogl, *Chem. Ber.* **98**, 2691 (1965).

^{189a} H. A. Staab and C. Wunsche, *Chem. Ber.* **98**, 3479 (1965).

¹⁹⁰ A. Alter, Belgian Patent 628,766 (1963); *Chem. Abstr.* **60**, 8044 (1964).

¹⁹¹ J. H. Biel and W. K. Hoya, U.S. Patent 3,141,015 (1965); *Chem. Abstr.* **61**, 8328 (1964).

¹⁹² P. Brookes, R. J. Terry, and J. Walker, *J. Chem. Soc.* p. 3165 (1957).

¹⁹³ R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *J. Med. Pharm. Chem.* **5**, 944 (1962).

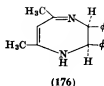
¹⁹⁴ Rhone-Poulenc S. A., Belgian Patent 618,068 (1962); *Chem. Abstr.* **59**, 6370 (1963).

¹⁹⁵ W. A. Schuler, H. Beschke, and A. von Schlichtegroll, U.S. Patent 3,040,043 (1962); *Chem. Abstr.* **57**, 13772 (1962).

¹⁹⁶ S. L. Shapiro, L. Friedman, and H. Soloway, Belgian Patent 617,599 (1962); *Chem. Abstr.* **59**, 646 (1963).

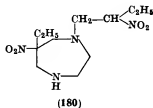
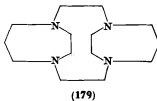
¹⁹⁷ J. H. Short, U. Biermacher, D. A. Dunnigan, and T. D. Leth, *J. Med. Chem.* **6**, 275 (1963).

¹⁹⁸ A. W. Weston and A. H. Sommers, U.S. Patent 2,655,498 (1953); *Chem. Abstr.* **48**, 12815 (1954).



they resemble the reactions of piperazine and were largely used to synthesize analogs of medicinally active compounds.

A convenient conversion of homopiperazine into the 1-methyl derivative involves reductive methylation with formaldehyde and a Raney nickel catalyst.^{199,199a} A small amount of the 1,4-dimethyl derivative is also obtained in this reaction. Use of benzaldehyde with homopiperazine gave **177** which was hydrolyzed to starting materials with hydrochloric acid.¹⁹⁹ Pyrolysis of the dihydrobromide of **148** ($R = H$, $R' = CH_2CH_2Br$) gave **178**, **179**, homopiperazine, and piperazine.¹⁴⁹



Treatment of the hydrochloride of **151** with warm ethanol gave partial hydrolysis to **180**. Further hydrolysis of **180** or its *N*-nitroso derivative gave the hydrochloride of **152**.^{155,156}

Lithium aluminum hydride reduction of **156** ($R = CH_3$ or $CH_2C_6H_5$) and **158** ($R^2 = R^6 = H$, $R = R^3 = R^4 = R^5 = CH_3$) gave the 1-substituted

¹⁹⁹ F. Poppelsdorf, R. C. Myerly, and R. G. Conrow, *J. Org. Chem.* **26**, 4138 (1961).

^{199a} F. Poppelsdorf, U.S. Patent 3,210,336 (1965); *Chem. Abstr.* **64**, 745 (1966).

homopiperazine.¹⁶¹⁻¹⁶⁴ The secondary nitrogen reacted in a normal manner with a variety of reagents.^{161, 162}

The structure of various homopiperazinones was generally proven by ring opening reactions under acidic conditions.^{160, 163, 165, 166, 169} Treatment of **158** ($R^2 = C_6H_5$, $R^5 = CH_3$, $R = R^3 = R^4 = R^6 = H$) with methyl iodide gave **181** ($R = C_6H_5$) which could be reduced with lithium aluminum hydride to 1-methyl-6-phenylhomopiperazine or opened to **182** ($R = C_6H_5$) through the Hofmann reaction.¹⁶⁶ The



(181)



(182)



(183)



(184)



(185)



(186)

quaternary salt (**181**, $R = H$) was also subjected to the Hofmann reaction to give a similar product.²⁰⁰ In a similar manner the methiodide of **183** gave **184** under the conditions of the Hofmann reaction.²⁰⁰

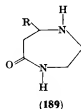
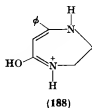
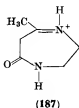
Use of excess *N*-(2-aminoisobutyl)isopropylamine in the preparation of **162** ($R = C_6H_5$) led to the opening of the seven-membered ring followed by ring closure to an imidazolidone (**185**) and a 2-imidazoline (**186**).¹⁷²

Protonation of **169** ($R = CH_3$) is interpreted on the basis of the ultraviolet spectra as giving **187** through protonation on C-6.¹⁸⁰ The compound **169** ($R = C_6H_5$), however, is believed to protonate on oxygen to give **188**¹⁸⁰ which would be expected to be resonance-stabilized by contributing forms in which each of the hetero atoms and the benzene ring bear a part of the positive charge. Catalytic hydrogenation of **169** gave the hexahydrodiazepinones (**189**).¹⁸⁰

²⁰⁰ L. A. Paquette and L. D. Wise, *J. Org. Chem.* **30**, 228 (1965).

In a study of the polymerization of lactams it was noted that **156** (R = benzenesulfonyl) did not polymerize.¹⁸³

Bromination of 2,3-dihydro-5,7-dimethyl-1,4-diazepine (**164**) or its salts led to the 6-bromo compound as evidenced by the hydrolysis of this product to 3-bromoacetylacetone.²⁰¹ The bromine can be readily



displaced by alkoxide and the presence of the 6-bromo or alkoxy substituents causes little change in the form of the ultraviolet spectra although there is a bathochromic displacement of the main peak.²⁰¹ The kinetics of the bromination of the perchlorate of **164** indicate that the reaction is a simple bimolecular reaction between the cation and bromine.²⁰² The cation of **164**, pK 13.4,²⁰³ appears to be in the form **190** on the basis of NMR evidence.¹⁸⁷ (But see footnote 180b.)



B. 1,4-BENZODIAZEPINES

The 1,4-benzodiazepines have recently been the subject of an excellent exhaustive review²⁰⁴ and this section will be concerned only with the work reported since that review. The major impedus for the wealth of work in this area has been the tranquilizer drug chlor-diazepoxide (**191**).

²⁰¹ D. Lloyd and D. R. Marshall, *J. Chem. Soc.* p. 118 (1958).

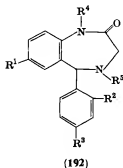
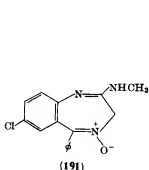
²⁰² R. P. Bell and D. R. Marshall, *J. Chem. Soc.* p. 2195 (1964).

²⁰³ G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta* **23**, 1162 (1940).

²⁰⁴ S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.* **53**, 577 (1964).

Using previously reported procedures a series of 1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (**192**) were prepared.²⁰⁵ Because of the differences in basicity between the two nitrogen atoms, it was found possible to alkylate the 1-nitrogen independently of the 4-nitrogen and vice versa.²⁰⁵

A reported²⁰⁶ preparation of 5*H*-1,4-benzodiazepin-5-ones from 2-amino-*N*-(2-hydroxyalkyl)benzamides has been shown to lead to oxazolines rather than to benzodiazepines.^{207, 208}



Derivatives of 1-methyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (**193**) were synthesized by ring closure of substituted 2-(*N*-chloroacetyl-*N*-methylamino)benzamides with sodium methoxide in methanol.²⁰⁹ Treatment of **193** with lithium aluminum hydride led to reduction of both carbonyl groups.²⁰⁹ The parent tetrahydro system (**194**) has been prepared by reaction of the tosylate (**195**) with 1,2-dibromoethane followed by hydrolysis.²¹⁰ The preparation of **194** by another route had previously been noted.²⁰⁴ Reaction of **194** with formaldehyde or benzaldehyde gave a compound formulated as **196** ($R = H$ or C_6H_5).²¹⁰ Hydrolysis of **196** ($R = C_6H_5$) with 0.1 *N* hydrochloric acid gave **194** while **196** ($R = H$) was not hydrolyzed at this acidity.

²⁰⁵ R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.* **7**, 386 (1964).

²⁰⁶ A. A. Santilli and T. S. Osden, *J. Org. Chem.* **29**, 1998 (1964).

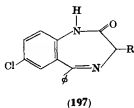
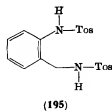
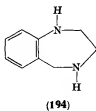
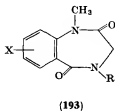
²⁰⁷ G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.* **30**, 2098 (1965).

²⁰⁸ A. A. Santilli and T. S. Osden, *J. Org. Chem.* **30**, 2100 (1965).

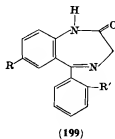
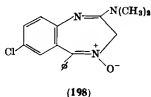
²⁰⁹ C. M. Lee, *J. Heterocyclic Chem.* **1**, 235 (1964).

²¹⁰ S. Shiotani and K. Mitsuhashi, *Yakugaku Zasshi* **84**, 656 (1964); *Chem. Abstr.* **61**, 10685 (1964).

Gentle warming of 2-acetamido-2-amino-2'-benzoyl-4'-chloroacetanilide resulted in the formation of diazepine (197, R = NHCOCH₃).²¹¹ Methanolysis of the acetyl group was accomplished at room tempera-



ture with hydrochloric acid catalysis to afford the 3-amino derivative (197, R = NH₂) which with nitrous acid gave the known alcohol (197, R = OH).²¹¹



Although the reaction of 2-chloromethyl-4-phenylquinazoline-3-oxides with primary amines led to a rearrangement to diazepines, the reaction with secondary amines has been reported to give only the normal quinazoline product.²⁰⁴ It has now been observed, however,

²¹¹ S. C. Bell, R. J. McCaully, and S. J. Childress, *Tetrahedron Letters* p. 2889 (1965).

that 6-chloro-2-chloromethyl-4-phenylquinazoline with dimethylamine leads to **198** as well as to the quinazoline derivative.²¹²

Reaction of **199** and its *N*-oxide with chloramine leads to the introduction of an amino group on the 1-nitrogen. Treatment of these 1-amino compounds with acid led to hydrolysis to 3-phenylindazoles.²¹³

Nitration of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one led to 7-nitro derivatives while 7-substituted compounds were nitrated in the 5-phenyl substituent.²⁰⁴ Nitration of the corresponding 7-unsubstituted 1,3,4,5-tetrahydro compound, however, occurs in the 5-phenyl substituent.²¹⁴

The oxidation of 2,3-dihydro and 1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepine derivatives has been investigated. Oxidation of compounds of the type **192** ($R^4 = R^5 = H$) with chromium trioxide in glacial acetic acid gave compounds of the type **199**.^{214, 215} Similar results were obtained with selenium dioxide or silver oxide.²¹⁵ Oxidation of the 1-methyl analog of **192** gave the 2,3(1*H*)dione.²¹⁵ Oxidation of 2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine also gave (**199**).²¹⁵

Substituted 1,4-benzodiazepine-4-oxides have been observed to undergo various rearrangements and transformations.²⁰⁴ Acetylation of **191** gave three products: the normal *N*-acetyl derivatives, a 3-acetoxy compound produced by rearrangement of the *N*-oxide, and the diacetyl compound (**200**).²¹⁶ The 1,4-benzodiazepines bearing an oxygen in position 3 rearranged in acidic medium to the corresponding 2-quinazolinecarboxaldehyde (for example, **201** to **202**),²¹⁶ thus demonstrating the potential aldehydic character of C-3. Alkaline hydrolysis of a system with an oxygen in position 3 has led to the formation of 3-phenylindole-2-carboxaldehyde.²¹⁷

Yet another rearrangement occurs in this system, when **203**

²¹² S. Farber, H. W. Wuest, and R. I. Meltzer, *J. Med. Chem.* **7**, 235 (1964).

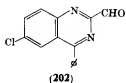
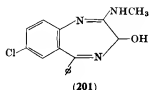
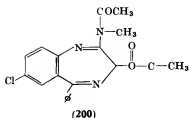
²¹³ W. Metlesics, R. F. Tavares, and L. H. Sternbach, *J. Org. Chem.* **30**, 1311 (1965).

²¹⁴ R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.* **30**, 521 (1965).

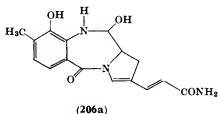
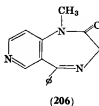
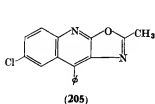
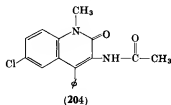
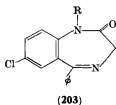
²¹⁵ R. I. Fryer, G. A. Archer, B. Brust, W. Zally, and L. H. Sternbach, *J. Org. Chem.* **30**, 1308 (1965).

²¹⁶ L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Racklin, *J. Org. Chem.* **29**, 332 (1964).

²¹⁷ W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.* **29**, 1621 (1964).



(R = CH₃) was treated with acetic anhydride in the presence of sodium acetate. This reaction led to the formation of the quinoline derivative (204).²¹⁸ With 203 (R = H) the rearrangement occurs to give 205 as



²¹⁸ R. I. Fryer and L. H. Sternbach, *J. Org. Chem.* **30**, 524 (1965).

the major product. Reasonable mechanisms have been proposed for these transformations.²¹⁸

The analogous 1,3-dihydro-1-methyl-5-phenyl-2*H*-pyrido(4,3-*e*)-1,4-diazepin-2-one (**206**) as well as the three other isomeric pyrido-diazepinones and the corresponding intermediates have been prepared.²¹⁹

The interest in compounds with potential medicinal activity has stimulated the appearance of a number of additional reports on 1,4-benzodiazepines.^{219a} The antibiotic anthramycin has been recently shown to be a 1,4-benzodiazepine derivative (**206a**).^{219b}

C. 1,5-BENZODIAZEPINES

1. *Synthesis*

The simple 1,5-benzodiazepine system (**207**, R = R' = H) has been prepared by reaction of 1,3-dibromopropane with the ditosylate of *o*-phenylenediamine.^{220, 221} This reaction leads to **207** (R = R' = tosyl) which can be hydrolyzed directly to **207** (R = R' = H).²²⁰ Partial hydrolysis of the tosylate led to **207** (R = H, R' = tosyl) which on further hydrolysis gave the parent compound.²²¹ In a similar manner the dipotassium salt of *o*-phenylenediamine ditosylate and 1,3-dibromoacetone gave **208**.²²² Treatment of **208** with base gave a deep red product for which structure **209** is favored.

The condensation of *o*-phenylenediamine with β -ketoesters has been studied by several groups of investigators. In the case of ethyl acetate the reaction yielded several products, among them the

²¹⁹ R. Littell and D. S. Allen, Jr., *J. Med. Chem.* **8**, 722 (1965).

^{219a} J. Iacobelli, M. Uskokovic, and W. Wenner, *J. Heterocyclic Chem.* **2**, 323 (1965); A. Stempel, E. Reeder, and L. H. Sternbach, *J. Org. Chem.* **30**, 4267 (1965); S. Hayao, J. H. Haver, W. G. Strycker, T. J. Leipzig, R. A. Kulp, and H. E. Hartzler, *J. Med. Chem.* **8**, 807 (1965); L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasylw, L. O. Randall, and R. Banziger, *J. Med. Chem.* **8**, 815 (1965); R. Littell and D. S. Allen, Jr., *J. Med. Chem.* **8**, 892 (1965); P. M. Carabateas and L. S. Harris, *J. Med. Chem.* **9**, 6 (1966); J. Krapcho and C. F. Turk, *J. Med. Chem.* **9**, 191 (1966); M. Müller and P. Zeller, *Helv. Chim. Acta* **49**, 1222 (1966).

^{219b} W. Leingruber, A. D. Batcho, and F. Schenker, *J. Am. Chem. Soc.* **87**, 5793 (1965).

²²⁰ O. Hinsberg and A. Strupler, *Ann. Chem.* **287**, 220 (1895).

²²¹ H. Stetter, *Chem. Ber.* **86**, 197 (1953).

²²² W. Paterson and G. R. Proctor, *J. Chem. Soc.* p. 485 (1965).

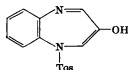
benzodiazepine (**210**, $R = CH_3$) (or, more likely, **211**, $R = CH_3$).²²³⁻²²⁵ The same benzodiazepine was also obtained from reaction of *o*-phenylenediamine with diketene.²²⁶ Other *o*-phenylenediamines with diketene gave products of similar structure.²²⁷ The same type product (**211**) was also obtained through reaction of *o*-phenylenediamine with β -ketoesters^{223, 228-231} and through reaction of 1,2-diaminonaphthalene or 2,3-diaminopyridine with ethyl acetoacetate, ethyl benzoylacetate, and nicotinoylacetic ester.^{228, 232} Although γ -phenylacetoacetic ester gave **211** ($R = CH_2C_6H_5$), α -phenylacetoacetic ester gave



(207)



(208)



(209)

only 1- β -methylstyrylbenzimidazole-2-one.²³⁰ When **212** and *o*-phenylene-diamine were refluxed in xylene or when **213** was refluxed in xylene, **211** ($R = CH_2CO_2R'$), together with a benzimidazole, was obtained.²³³

In addition to β -ketoesters, both β -diketones and β -diesters react with *o*-phenylenediamine. Acetylacetone condenses under acidic conditions to give a colored salt represented as **214** or **215**, which yields a colorless base (**216**, $R = R' = CH_3$, or **217**, $R = R' = CH_3$).²³⁴ Other workers have repeated this same reaction and also have used a variety

²²³ J. Davoll, *J. Chem. Soc.* p. 308 (1960).

²²⁴ A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim. Acta* **43**, 1298 (1960).

²²⁵ W. A. Sexton, *J. Chem. Soc.* p. 303 (1942).

²²⁶ W. Ried and P. Stahlhofen, *Chem. Ber.* **90**, 825 (1957).

²²⁷ W. Ried and E. Torinus, *Chem. Ber.* **92**, 2902 (1959).

²²⁸ V. R. Barchet and K. W. Merz, *Tetrahedron Letters* p. 2239 (1964).

²²⁹ W. Ried and P. Stahlhofen, *Chem. Ber.* **90**, 828 (1957).

²³⁰ A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim. Acta* **43**, 1046 (1960).

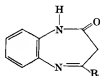
²³¹ F. B. Wigton and A. Joullie, *J. Am. Chem. Soc.* **81**, 5212 (1959).

²³² W. Ried and W. Hohne, *Chem. Ber.* **87**, 1801 (1954).

²³³ K. W. Merz, R. Haller, and E. Mueller, *Naturwissenschaften* **50**, 663 (1963).

²³⁴ J. Thiele and G. Steimmig, *Ber. Deut. Chem. Ges.* **40**, 995 (1907).

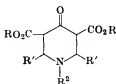
of other β -diketones or malondialdehydes.^{235-251a} A variety of substituted diamines have also been used.^{232, 243} The reaction has been suggested as a colorimetric determination of acetylacetone.²⁵¹ *N*-Methyl or *N,N'*-dimethyl-*o*-phenylenediamines with 1,3-dicarbonyl compounds or unsaturated ketones gave only benzimidazoles.²⁵²



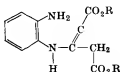
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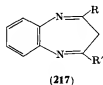
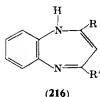
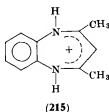
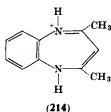
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- ²³⁵ R. M. Acheson, *J. Chem. Soc.* p. 4731 (1956).
²³⁶ J. A. Barltrop and C. G. Richards, *Chem. Ind. (London)* p. 466 (1957).
²³⁷ A. Becker, *Helv. Chim. Acta* **32**, 1584 (1949).
²³⁸ B. Emmert and H. Gsottschneider, *Ber. Deut. Chem. Ges.* **66**, 1871 (1933).
²³⁹ I. L. Finar, *J. Chem. Soc.* p. 4094 (1958).
²⁴⁰ T. N. Ghosh, *J. Indian Chem. Soc.* **15**, 89 (1938).
²⁴¹ C. A. C. Haley and P. Maitland, *J. Chem. Soc.* p. 3155 (1951).
²⁴² F. E. King and P. C. Spensley, *J. Chem. Soc.* p. 2144 (1952).
²⁴³ D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc.* p. 3785 (1965).
²⁴⁴ J. Perello, J. Bartulin, and H. Urrutia, *Bol. Soc. Chilena Quim.* **10**, 18 (1960); *Chem. Abstr.* **56**, 5907 (1962).
²⁴⁵ H. Rupe and A. Huber, *Helv. Chim. Acta* **10**, 846 (1927).
²⁴⁶ W. Ruske and E. Hufner, *J. Prakt. Chem.* [4], **18**, 156 (1962).
²⁴⁷ W. H. Stafford, D. H. Ried, and P. Barker, *Chem. Ind. (London)* p. 765 (1956).
²⁴⁸ S. B. Vaisman, *Trans. Inst. Chem. Kharkov Univ.* **4**, 157 (1938); *Chem. Abstr.* **34**, 5847 (1940).
²⁴⁹ S. B. Vaisman, *Tr. Inst. Khim. Kharkov Gosudarst. Univ.* **5**, 57 (1940); *Chem. Abstr.* **38**, 750 (1944).
²⁵⁰ S. Veibel and S. F. Hromadko, *Chem. Ber.* **93**, 2752 (1960).
²⁵¹ R. F. Witter, J. Snyder, and E. Stotz, *J. Biol. Chem.* **176**, 493 (1948).
^{251a} Y. K. Yurev, N. N. Magdesieva, and V. V. Titov, *Zhur. Org. Khim.* **1**, 163 (1965).
²⁵² W. Ruske and G. Grimm, *J. Prakt. Chem.* [4], **18**, 163 (1962).

Cyclization of 4-*N*-(*o*-methylaminophenyl)iminopentanone-2 (from *N*-methyl-*o*-phenylenediamine and acetylacetone), however, gave 1,2,4-trimethyl-1,5-benzodiazepine.²⁵³



Condensation of two tetraketones with *o*-phenylenediamine gave the diazepines **218**.²⁵⁹ Reaction of **219** (R = OEt) with *o*-phenylenediamine gave **220**, while **219** (R = SEt) gave **221**.²⁵⁴

Diazepines of the type **222** have been obtained in low yield in addition to benzimidazoles in reactions of aromatic aldehydes with *o*-phenylenediamines.²⁵⁵⁻²⁶⁰

Reaction of *o*-phenylenediamine with malonic acid in the presence of hydrochloric acid gave the diazepine **223** (R¹ = R² = R³ = R⁴ = H).²⁶¹⁻²⁶⁵ Substituted malonic esters have also been used to give

²⁵³ J. O. Halford and R. M. Fitch, *J. Am. Chem. Soc.* **85**, 3354 (1963).

²⁵⁴ H. D. Stachel, *Chem. Ber.* **95**, 2172 (1962).

²⁵⁵ N. V. S. Rao and C. V. Ratnam, *Current Sci. (India)* **24**, 299 (1955).

²⁵⁶ N. V. S. Rao and C. V. Ratnam, *Proc. Indian Acad. Sci.* **43A**, 173 (1956).

²⁵⁷ N. V. S. Rao and C. V. Ratnam, *Proc. Indian Acad. Sci.* **44A**, 331 (1956).

²⁵⁸ N. V. S. Rao and C. V. Ratnam, *Proc. Indian Acad. Sci.* **45A**, 253 (1957).

²⁵⁹ N. V. S. Rao and C. V. Ratnam, *Proc. Indian Acad. Sci.* **47A**, 77 (1958).

²⁶⁰ S. Weil and H. Marcinkowska, *Roczniki Chem.* **14**, 1312 (1934).

²⁶¹ J. Buchi, H. Dietrich, and E. Eichenberger, *Helv. Chim. Acta* **39**, 957 (1956).

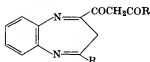
²⁶² R. Meyer, *Ann. Chem.* **347**, 17 (1906).

²⁶³ R. Meyer and H. Laders, *Ann. Chem.* **415**, 29 (1918).

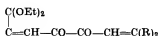
²⁶⁴ M. A. Phillips, *J. Chem. Soc.* p. 2393 (1928).

²⁶⁵ R. L. Shriner and P. G. Boermans, *J. Am. Chem. Soc.* **66**, 1810 (1944).

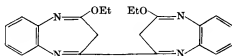
compounds of the type **223** ($R^1 = R^2 = H$).^{261, 266} Use of α, β -unsaturated acids with *o*-phenylenediamine gave rise to diazepines of the type **224**.^{223, 267-269} Similar reactions took place with 1,2-diaminonaphthalene.²³²



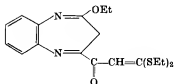
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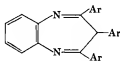
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(220)



(221)



(222)

A number of α, β -unsaturated ketones^{227, 270-272} and β -halo-ketones^{227, 270} have been condensed with *o*-phenylenediamine to give diazepines (**225**, $R^4 = H$). Use of *N*-phenyl-*o*-phenylenediamine gave **225** ($R^4 = C_6H_5$) and **226**.²⁷⁰ The reaction of mesityl oxide with *o*-phenylenediamine had been reported²⁷³ to give a benzimidazole; however, investigation of the product by NMR indicates that it has structure **225** ($R^1 = R^2 = R^3 = CH_3$, $R^4 = H$).²⁷⁴

²⁶⁶ A. S. Fenton, A. M. Creighton, and R. Wragg, U.S. Patent 3,133,056 (1964); *Chem. Abstr.* **61**, 8326 (1964).

²⁶⁷ G. B. Bachman and L. V. Heisey, *J. Am. Chem. Soc.* **71**, 1985 (1949).

²⁶⁸ S. H. Dandegaonker and G. B. Desai, *Indian J. Chem.* **1**, 298 (1963).

²⁶⁹ W. Ried and G. Urllass, *Chem. Ber.* **86**, 1101 (1953).

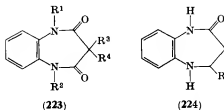
²⁷⁰ L. K. Mushkalo, *Nauk Zap., Kiivs'k. Derzh. Univ.* **16**, No. 15, *Zs'kirnik Khim. Fak.* No. 8, 133 (1957); *Chem. Abstr.* **53**, 18057 (1959).

²⁷¹ W. Ried and P. Stahlhofen, *Chem. Ber.* **90**, 815 (1957).

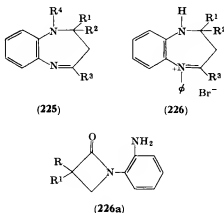
²⁷² J. Sprague, PB Rept. 135342; *Chem. Abstr.* **54**, 12155 (1960).

²⁷³ R. C. Elderfield and J. R. McCarthy, *J. Am. Chem. Soc.* **73**, 975 (1951).

²⁷⁴ J. W. Clark-Lewis, J. A. Edgar, J. S. Shannon, and M. J. Thompson, *Australian J. Chem.* **17**, 877 (1964).



Compounds of the type **224** ($R = CH_3$) have been prepared by catalytic hydrogenation of nitroacetoacetanilides.^{274a} The 4-membered **226a** were converted by intramolecular transamidation to the corresponding diazepines.^{274b}



2. Reactions

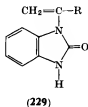
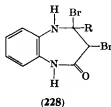
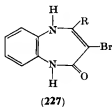
Catalytic hydrogenation of **211** led to the formation of **224**^{223, 224, 226-230} whose direct preparation is described in Section IV, C, 1. Bromination of **211** ($R = C_6H_5$ or 3-pyridyl) led to the formation of the 6-bromo derivative (**227**)²²⁸ apparently through the intermediate **228**.

Treatment of **211** ($R = CH_3$) with a catalytic amount of sodium 2-ethoxyethoxide gave **229**²²³ while **211** ($R = C_6H_5$) also gave **229**.²²⁸ Acid hydrolysis of **211** ($R = CH_3$ or C_6H_5) gave acetone and 2-methylbenzimidazole or acetophenone and 2-phenylbenzimidazole.²²³ A

^{274a} J. Hornyna, Czechoslovakian Patent 113,422 (1965); *Chem. Abstr.* **63**, 18129 (1965).

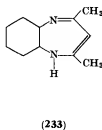
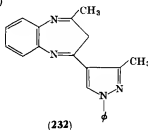
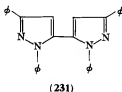
^{274b} B. J. R. Nicolaus, E. Bellasio, G. Pagani, L. Mariani, and E. Testa, *Helv. Chim. Acta* **48**, 1867 (1965).

number of other reactions of these compounds have been studied.^{223, 231} Acid or base (25% potassium hydroxide) hydrolysis of **211** ($R = CH_2CO_2R'$) gave *o*-phenylenediamine and acetone while treatment with 8% potassium hydroxide gave **211** ($R = CH_3$)²³³. Treatment of **210** ($R = CF_3$) with hydroxylamine gave 3-(*o*-amino-phenylimino)-4,4,4-trifluorobutyrohydroxamic acid.²³¹



Compounds of the type **210** were alkylated by dialkylaminoalkyl chlorides in the presence of sodium amides.²⁷⁵

Reaction of phenylhydrazine with compounds of the type **217** gave **230**.²³⁹ With **218** ($R = C_6H_5$), **231** was obtained and with **218** ($R = CH_3$), **232** was obtained.²³⁹ Reaction of **217** ($R = CH_3$, $R' = CH_3$ or C_6H_5)

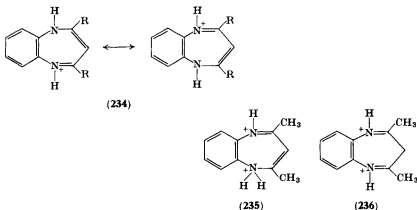


with diethyl oxalate in the presence of potassium gave a diazabenzobenzazulene derivative via reaction of the oxalate with the methyl group.²⁶⁰ Attempts to prepare **217** through dehydrogenation of **207** or **233** failed.²⁴³

²⁷⁵ L. H. Werner, U.S. Patent 2,957,867 (1960); *Chem. Abstr.* **55**, 7451 (1961).

A detailed discussion of the stability of trimethyl-1,5-benzodiazepines and their salts has appeared.²⁵³

A considerable effort has been devoted to the study of the tautomerism of **216** versus **217**.^{187, 201, 236, 239, 246, 248, 249, 276-280} The infrared work supports **217**²⁴⁵ and a recent NMR study,²⁷⁹ which also summarizes some of the work of others, indicates that **217** is indeed the structure. The colored salt derived from **217** can be represented as **215** or **234**.²⁷⁹ Diprotonation occurs in concentrated acids (pK_1 about -1) to give the colorless ion **235**²⁴³ or, as indicated by NMR, **236**.¹⁸⁷



Decomposition of the benzodiazepinium salts (**234**) leads to benzimidazoles and ketones.²⁴³

Treatment of **223** ($R^1 = R^2 = H$) with potassium hydroxide and alkyl bromides gave the *N*- and *N,N*-disubstituted compounds.²⁶¹ The reaction of **223** ($R^1 = R^2 = R^3 = R^4 = H$) with methyl iodide and sodium ethoxide gave an *N,N'*-dimethyl compound which on treatment with dilute sulfuric acid and then potassium hydroxide gave **237**.²⁶⁵ The ultraviolet spectrum of **223** has been studied but no conclusions have been reached in regard to the tautomerism.²⁸¹ The

²⁷⁶ J. A. Barltrop and C. G. Richards, *Chem. Ind. (London)* p. 1011 (1957).

²⁷⁷ J. A. Barltrop, C. G. Richards, and D. M. Russell, *J. Chem. Soc.* p. 1423 (1959).

²⁷⁸ J. A. Barltrop, C. G. Richards, D. M. Russell, and G. Ryback, *J. Chem. Soc.* p. 1132 (1959).

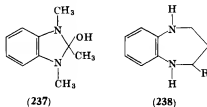
²⁷⁹ W. J. Barry, I. L. Finar, and E. F. Mooney, *Spectrochim. Acta* **21**, 1095 (1965).

²⁸⁰ G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta* **23**, 1147 (1940).

²⁸¹ G. Glotz, *Bull. Soc. Chim. France* [5], **3**, 511 (1936).

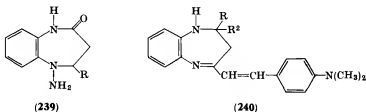
compound **223** ($R^1 = R^2 = \text{CH}_3$, $R^3 = R^4 = \text{C}_2\text{H}_5$) has shown good analgesic action.²⁶¹

Lithium aluminum hydride reduction of **224** gave the tetrahydro compound **238**.²²³ Compounds of the type **224** ($R = \text{aryl}$) formed semicarbazones,²⁶⁸ while **224** ($R = \text{H}$ or CH_3) could be nitrosated and the *N*-nitroso group reduced to an amino group.²⁸² These amines



(**239**) reacted with aldehydes in the normal manner.²⁶⁹ Carbamyl derivatives of **224** have also been prepared.²⁸³

Reaction of compounds of the type **225** ($R^3 = \text{CH}_3$) with *p*-dimethylaminobenzaldehyde in pyridine or acetic anhydride gave **240**,²⁷⁰ while the same compound with ethyl orthoformate gave a trimethine cyanine.²⁷⁰



D. DIBENZO COMPOUNDS

1. Synthesis

A number of 5*H*-dibenzo(*b,e*)-1,4-diazepines (**241**) have been prepared by treatment of **242** with polyphosphoric acid.^{284, 285, 285a}

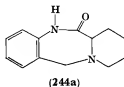
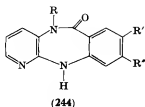
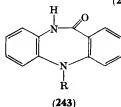
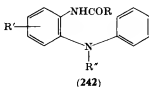
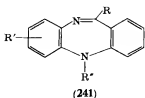
²⁸² W. Ried and A. Draisbach, *Chem. Ber.* **92**, 949 (1959).

²⁸³ O. E. Fancher, G. Nichols, and D. A. Stauffer, U.S. Patent 3,021,325 (1962); *Chem. Abstr.* **57**, 4687 (1962).

²⁸⁴ F. Hunziker, F. Kunzle, O. Schindler, and J. Schmutz, *Helv. Chim. Acta* **47**, 1163 (1964).

²⁸⁵ F. Hunziker, F. Kunzle, and J. Schmutz, *Helv. Chim. Acta* **46**, 2337 (1963).

^{285a} F. Hunziker, F. Kunzle, and J. Schmutz, *Helv. Chim. Acta* **49**, 244 (1966).



Heating of *N*-(*o*-aminophenyl)anthranilic acid^{286, 287} or its *N*-alkyl derivatives²⁸⁸⁻²⁹⁰ gave rise to the lactams (243). The parent lactam (243, R = H) was also obtained in good yield by heating the methyl ester of *N*-(*o*-aminophenyl)anthranilic acid.²⁹¹ Similarly a variety of dialkylaminoalkyl-substituted analogs (243, R = C_nH_{2n}NR'R'') were prepared from the *N*-alkylated anthranilates.²⁹¹

The aza analog (244) has also been prepared,^{292, 292a} as has 244a.^{292b}

²⁸⁶ G. R. Clemo, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **125**, 1779 (1924).

²⁸⁷ A. M. Monro, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.* **6**, 255 (1963).

²⁸⁸ H. Burton and C. S. Gibson, *J. Chem. Soc.* **125**, 2501 (1924).

²⁸⁹ F. Hunziker, H. Lauener, and J. Schmutz, *Arzneimittel-Forsch.* **13**, 324 (1963).

²⁹⁰ W. H. Linnell and W. H. Perkin, Jr., *J. Chem. Soc.* **125**, 2451 (1924).

²⁹¹ A. R. Hanze, R. E. Strube, and M. E. Greig, *J. Med. Chem.* **6**, 767 (1963).

²⁹² G. Schmidt, German Patent 1,179,943 (1964); *Chem. Abstr.* **62**, 1677 (1965).

^{292a} G. Schmidt, German Patent 1,204,680 (1965); *Chem. Abstr.* **64**, 3578 (1966).

^{292b} J. R. Geigy A. G., Neth. Appl. 6,503,749 (1965); *Chem. Abstr.* **64**, 8221 (1966).

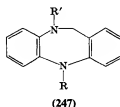
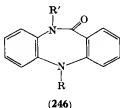
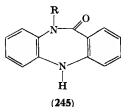
^{292c} F. Hunziker and O. Schindler, *Helv. Chim. Acta* **48**, 1590 (1965).

^{292d} G. Schmidt, German Patent 1,205,106 (1965); *Chem. Abstr.* **64**, 3576 (1966).

2. Reactions

Diazepine **243** ($R=H$) gave a monoacetyl and a nitroso derivative.²⁸⁶ Alkylation of **243** ($R=H$) with sodamide and dialkylamino-alkyl chlorides in dioxane substitutes only at the 10-position to give **245**,^{289, 291} while alkylation of **243** [$R=(CH_2)_2N(C_2H_5)_2$] gave **246**. This same type reaction has been used to introduce a labeled side chain into **246**.^{292d}

Reduction of **241**, **243**, and **245** with lithium aluminum hydride gave the corresponding reduced ring structures (**247**).^{285, 285b, 291} Reduction of (**244**)^{292d} and (**244a**)^{292b} proceeded in a similar manner. On treatment with mercuric acetate **247** could be converted into **241**.²⁸⁵



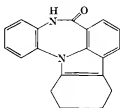
Acylation of **243** ($R=H$) with chloroacetyl and chloropropionyl chlorides gave **245** [$R=CO(CH_2)_nCl$] in which the chlorines could then be displaced by alkylamines.²⁸⁷ Reduction of these dialkylamino compounds with lithium aluminum hydride gave interesting results. Compound **245** ($R=COCH_2NMe_2$) underwent hydrogenolysis to give **243** ($R=H$) in poor yield. Compound **245** ($R=COCH_2CH_2NEt_2$), gave the desired compound **247** [$R=H$, $R'=(CH_2)_3NEt_2$], while **245** ($R=COCH_2CH_2NMe_2$) gave a mixture of **247** [$R=H$, $R'=(CH_2)_3NMe_2$] and **243** [$R=(CH_2)_3NMe_2$].²⁸⁷

The ultraviolet spectrum of **247** ($R=R'=H$) is similar to that of *o*-aminodiphenylamine and a comparison of the two spectra indicates that in the case of **247** the restricting effect of the $-CH_2NH-$ bridge actually allows better conjugation than in the unbridged analog.²⁸⁷

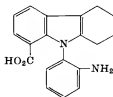
The nitroso derivative **243** ($R=NO$) is easily obtained from **243** ($R=H$). Reduction of this nitroso derivative in cyclohexanone gave **248** which was hydrolyzed by alkali to **249**.²⁹⁰

In tests for autonomic activity and for reserpine antagonism, several of the compounds described in this section showed activity comparable to that of the drug imipramine (a dibenzo(*b,f*)azepine).²⁸⁷

Additional pharmacological properties have been discussed.^{285, 291, 293} The patent literature also contains numerous references to the preparation of compounds of types **241**, **243**, **246**, and **247** as compounds of potential therapeutic properties.²⁹⁴⁻³⁰⁰



(248)



(249)

E. OTHER 1,4-DIAZEPINES

A number of cyclic β -ketoesters have been reacted with *o*-phenylenediamine to give analogs of compounds mentioned earlier. In this manner compounds of the type **250**,²²⁴ **251**,³⁰¹ **252**,³⁰² and **253**³⁰³ have been prepared. Treatment of **250** with sodium in cellosolve gave rise to **254**, while catalytic hydrogenation reduced the double bond in

²⁹³ H. Ackermann, E. Eichenberger, F. Hunziker, H. Lavener, and J. Schmitz, *Med. Exptl.* **6**, 205 (1962); *Chem. Abstr.* **57**, 11827 (1962).

²⁹⁴ Boots Pure Drug Co., Ltd., British Patent 738,013 (1955); *Chem. Abstr.* **50**, 13102 (1956).

²⁹⁵ Dr. A. Wander S. A., French Patent CAM51 (1964); *Chem. Abstr.* **61**, 8328 (1964).

²⁹⁶ Dr. A. Wander S. A., British Patent 907,646 (1962); *Chem. Abstr.* **58**, 11385 (1963).

²⁹⁷ Dr. A. Wander S. A., British Patent 959,994 (1964); *Chem. Abstr.* **61**, 12020 (1964).

²⁹⁸ Dr. A. Wander S. A., British Patent 961,105 (1964); *Chem. Abstr.* **61**, 5673 (1964).

²⁹⁹ Dr. A. Wander S. A., British Patent 961,106 (1964); *Chem. Abstr.* **61**, 13332 (1964).

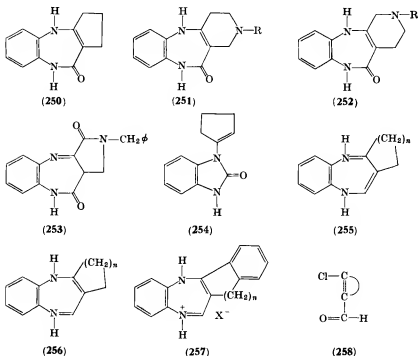
³⁰⁰ Parke, Davis and Co., Belgian Patent 611,926 (1962); *Chem. Abstr.* **57**, 13784 (1962).

³⁰¹ Chemische Fabrik Promonta G. M. B. H., British Patent 822,215 (1959); *Chem. Abstr.* **54**, 11062 (1960).

³⁰² R. Kallischnigg, German Patent 1,055,000 (1959); *Chem. Abstr.* **55**, 11448 (1961).

³⁰³ S. Morosawa, *Bull. Chem. Soc. Japan* **31**, 418 (1958); *Chem. Abstr.* **53**, 8160 (1959).

250.²²⁴ The compounds **255**, **256**, and **257** were prepared by the reaction of 2-hydroxymethylenecyclohexanones³⁰⁴ and β -chlorovinylaldehydes (as **258**)³⁰⁵ with *o*-phenylenediamine.



A number of diazepines have been prepared from 1,2-diamines such as 4,5-diaminopyrimidine,³⁰⁶ 2,4-diaminotroponimine,³⁰⁷ and *trans*-1,2-diaminocyclopentane³⁰⁸ with ethyl acetoacetate, nitromalondialdehyde, and acetylacetone, respectively.

Diazepines **259** and **260** have been prepared²⁸² by condensation of ethyl cyclohexanone-2-carboxylate with the appropriate diamine followed by cyclization of the initially formed imine.

³⁰⁴ M. Weissenfels, U. Thust, and M. Muehlstaedt, *J. Prakt. Chem.* [4], **20**, 117 (1963).

³⁰⁵ M. Weissenfels, *Z. Chem.* **4**, 458 (1964).

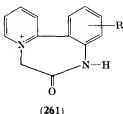
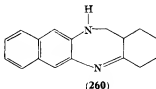
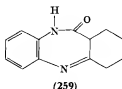
³⁰⁶ W. H. Nyberg, C. W. Noell, and C. C. Cheng, *J. Heterocyclic Chem.* **2**, 110 (1965).

³⁰⁷ W. Ruske, *J. Prakt. Chem.* [4], **18**, 173 (1962).

³⁰⁸ D. Lloyd and D. R. Marshall, *J. Chem. Soc.* p. 2597 (1956).

Use of 2-(*o*-aminophenyl)pyridines has led to the formation of **261**.³⁰⁹ The pyridine ring in these diazepines can be completely reduced by catalytic hydrogenation or partially reduced with sodium borohydride.³¹⁰

The reaction of diethyl acetylenedicarboxylate with 1,8-diaminonaphthalene gave the 2-oxo-3-ethoxycarbonylmethylene compound (**262**) and the corresponding 2,3-bis(ethoxycarbonyl) compound.³¹¹



Several complex diazepines have been prepared through Beckmann and Schmidt reactions.³¹²⁻³¹⁶ Treatment of the oxime (**263**) with acetic anhydride and sulfuric acid gave a product¹¹⁰ at one time believed to be **264**.³¹⁷ An independent synthesis of **264** has been carried out by cyclization of **265**¹¹⁵ and, although a direct comparison was not possible, it appears that **264** was not the product obtained from **263**.

³⁰⁹ P. H. Wei, U.S. Patent 3,184,448 (1965); *Chem. Abstr.* **63**, 7026 (1965).

³¹⁰ P. H. Wei, U.S. Patent 3,185,680 (1965); *Chem. Abstr.* **63**, 5663 (1965).

³¹¹ Y. Iwanami, *Nippon Kagaku Zasshi* **83**, 597 (1962); *Chem. Abstr.* **59**, 3920 (1963).

³¹² M. Harfenist and E. Magnien, *J. Am. Chem. Soc.* **80**, 6080 (1958).

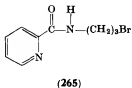
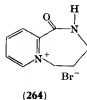
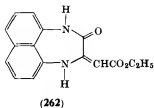
³¹³ T. Ichii, *Yakugaku Zasshi* **82**, 992 (1962).

³¹⁴ T. Ichii, *Yakugaku Zasshi* **82**, 999 (1962).

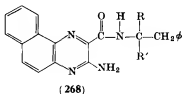
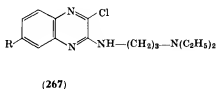
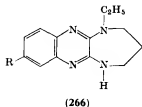
³¹⁵ P. I. Ittyerah and F. G. Mann, *J. Chem. Soc.* p. 467 (1958).

³¹⁶ J. G. Lombardino, W. M. McLamore, and G. D. Laubach, U.S. Patent 3,045,008 (1962); *Chem. Abstr.* **57**, 16640 (1962).

³¹⁷ L. Bauer and R. E. Hewitson, *J. Org. Chem.* **27**, 3982 (1962).



Two quinoxaline analogs (**266**) have been prepared by heating **267**.^{318, 319} In a similar manner **268** gave the expected diazepine derivative.³²⁰



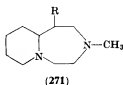
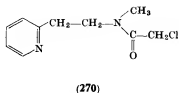
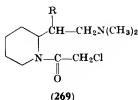
Ring closures of **269** and **270** in aqueous sodium bicarbonate led to the expected diazepinium salts.³²¹ These salts could through a simple sequence of reactions be converted into **271**.³²¹

³¹⁸ A. F. Crowther, F. H. S. Curd, D. G. Davey, and G. J. Stacey, *J. Chem. Soc.* p. 1260 (1949).

³¹⁹ R. D. Haworth and S. Robinson, *J. Chem. Soc.* p. 777 (1948).

³²⁰ A. A. Santilli and T. S. Osden, *J. Org. Chem.* **29**, 2066 (1964).

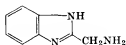
³²¹ F. F. Blicke and J. L. Hughes, *J. Org. Chem.* **26**, 3257 (1961).



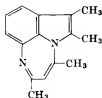
A number of conversions in the thiamine series have led to pyrimido(4,5-*e*)-1,4-diazepines.³²²

Reaction of **272** with acrylic acid, β -chlorobutyric acid, β -diketones, or α,β -unsaturated ketones gave the expected diazepines, while acetoacetic ester and diketene reacted only at the primary amino group.³²³ Similarly, **273** was obtained from acetylacetone and 2,3-dimethyl-7-aminoindole.³²⁴

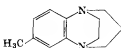
Although no convincing proof of structure has been offered it has been reported that 6-methyl-1,2,3,4-tetrahydroquinoxaline and 1,3-



(272)



(273)



(274)



(275)

³²² H. Hirano, *Yakugaku Zasshi* **77**, 1007 (1957); *Chem. Abstr.* **52**, 3828 (1958).

³²³ W. Ried and F. Grull, *Chem. Ber.* **96**, 130 (1963).

³²⁴ P. M. Maitlis, *Proc. Chem. Soc.* p. 354 (1957).

dibromopropane gave **274**³²⁵ and that piperazine with cyclohexanone-2-carboxylic acid gave **275**.³²⁶

A number of other complex diazepines with the nitrogens 1,4- have also been prepared.³²⁷⁻³³⁰

Note Added in Proof: Since the completion of this review the following additional reports have appeared:

1,2-Diazepines: E. E. Mikhlin, N. A. Komarova, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* **1966**, 259; *Chem. Abstr.* **65**, 717 (1966).

1,3-Diazepines: J. A. Bell and I. Dunstan, *J. Chem. Soc., C., Org.* p. 870 (1966); E. C. Taylor and J. G. Berger, *Abstr. Am. Chem. Soc. Meeting, Sept.*, 1966, p. P 53 (1965).

1,4-Diazepines: G. A. Archer, A. Stempel, S. S. Ho, and L. H. Sternbach, *J. Chem. Soc., C., Org.* p. 1031 (1966); A. M. Duffield, C. Djerassi, L. Wise, and L. A. Paquette, *J. Org. Chem.* **31**, 1599 (1966); G. F. Field, W. J. Zally, and L. H. Sternbach, *Tetrahedron Letters* p. 2609 (1966); M. Fraser, A. Molera, and D. H. Reid, *J. Chem. Soc., B., Phys. Org.* p. 483 (1966); R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Am. Chem. Soc.* **88**, 3173 (1966); N. D. Heindel, T. F. Lemke, H. R. Harless, and L. E. Brydia, *Abstr. Am. Chem. Soc. Meeting, Sept.*, 1966, p. P 57 (1965); M. Israel, L. C. Jones, and E. J. Modest, *Abstr. Am. Chem. Soc. Meeting, Sept.*, 1966, p. S 16 (1966); D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc., C., Org.* p. 780 (1966); M. Mueller and P. Zeller, *Helv. Chim. Acta* **49**, 1222 (1966); H. Oelschlaeger, J. Volke, and H. Hoffmann, *Coll. Czech. Chem. Comm.* **31**, 1264 (1966); G. S. Sidhu, G. Thyagarajan, and U. T. Bhalarao, *J. Chem. Soc., C., Org.* p. 969 (1966); Manufacture de Produits Pharmaceutiques A. Christiaens Soc. Anon., *Neth. Appl.* 6,508,663 (1966); *Chem. Abstr.* **64**, 15904 (1966).

³²⁵ T. S. Moore and I. J. Doubleday, *J. Chem. Soc.* **119**, 1170 (1921).

³²⁶ A. Kotz and B. Markel, *J. Prakt. Chem.* [2], **79**, 124 (1909).

³²⁷ E. Benary, *Ber. Deut. Chem. Ges.* **60**, 1826 (1927).

³²⁸ R. F. Homer and T. E. Tomlinson, *J. Chem. Soc.* p. 2498 (1960).

³²⁹ R. Punmerer and F. Meininger, *Ann. Chem.* **590**, 173 (1954).

³³⁰ F. M. Rowe, W. C. Dovey, B. Garforth, E. Levin, J. D. Pask, and A. T. Peters, *J. Chem. Soc.* p. 1796 (1935).

Phenoxazines

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R.S. Roumania, Cluj, Roumania*

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I. Introduction

Even before the first synthesis of phenoxazine—reported in 1887 by Bernthsen¹—two dyestuffs with the phenoxazine ring system, Meldola's blue and gallocyanine, were commercially available. After its discovery, however, the chemistry of the phenoxazines lay dormant for nearly half a century. Only during the last 10 years has this class of compound aroused renewed interest, as evidenced by the discovery of naturally occurring and biologically active phenoxazines.

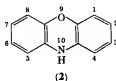
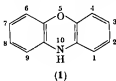
Aspects of the earlier phenoxazine literature are to be found in two previous reviews,^{2,3} and for the chemistry of phenoxazones (3*H*-

¹ A. Bernthsen, *Ber. Deut. Chem. Ges.* **20**, 942 (1887).

² D. E. Pearson, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, Chapt. 14, p. 685. Wiley, New York, 1957.

³ G. R. Ramage, E. H. Rodd, and J. K. Landquist, in "Chemistry of Carbon Compounds. IV C, Heterocyclic Compounds" (E. H. Rodd, ed.), Chapt. XVI. Elsevier, Amsterdam, 1960.

phenoxazin-3-ones)—the oxidation products of phenoxazines—the reader is referred to the more recent compilation of Schäfer.⁴ While the present review describes recent advances, it is intended also to give a general outline of the chemistry of phenoxazine. Effort has been made to include all relevant papers indexed by *Chemical Abstracts*, up to and including August, 1965.



Nomenclature and Numbering. Since the discovery of phenoxazine, apart from the inversion of the syllable "ox" with "az" (i.e., "phenazoxine") in a few older papers, this name has not suffered changes subsequently. However, it is most unfortunate that no general agreement has yet been reached concerning the method of numbering the phenoxazine system; this leads to much confusion and loss of time when searching the literature, especially for fused ring systems containing the phenoxazine nucleus.

From the different suggested numberings of the phenoxazine nucleus, at present only two systems, 1 and 2, are widely used. Throughout this paper the numbering system 1 has been adopted as being the most frequent today, and also approved in the "Revised Ring Index" (no. 3290),⁵ used in *Chemical Abstracts* and recommended by the "IUPAC Rules of Organic Nomenclature."⁶

However, system 2, based upon the numbering given by Bernthsen, and adopted in Beilstein's *Handbuch*, is still widely employed, especially in the German literature.

II. Methods of Preparation

The usual synthesis of phenoxazines makes use of suitable *ortho*-disubstituted benzenes, starting from which the oxazine skeleton is completed by ring closure. As intermediates, during the different ring

⁴ W. Schäfer, *Progr. Org. Chem.* **6**, 135 (1964).

⁵ A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed. Am. Chem. Soc., Washington, D.C., 1960.

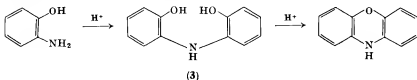
⁶ "IUPAC Rules of Organic Nomenclature," *Bull. Soc. Chim. France* p. 1258 (1958).

closure methods, either *o,o'*-disubstituted diphenylamines or *o,o'*-disubstituted diphenyl ethers have been isolated. From this observation we can establish two general approaches to the phenoxazine system. Further, substituents may be introduced into the already formed phenoxazine ring. This constitutes a third approach, which may involve electrophilic and nucleophilic substitution, or the modification of substituents in derivatives obtained by one of the two ring closures (see Section IV).

A. RING CLOSURE OF 2,2'-DISUBSTITUTED DIPHENYLAMINES

1. Autocondensation of *o*-Aminophenols

The classical method for preparing phenoxazines, based upon Bernthsen's first synthesis of phenoxazine, consisted in the pyrolytic condensation of *o*-aminophenols with catechols. Kehrmann and Neil⁷ pointed out, as early as 1914, that phenoxazine can be obtained with



good yield simply on heating an equimolar mixture of *o*-aminophenol and *o*-aminophenol hydrochloride without catechol. It was demonstrated later that the pyrolytic reaction takes place always between two molecules of *o*-aminophenol and that the catechol acts only as proton donor; experimental evidence for this was obtained by the isolation of the intermediate 2,2'-dihydroxydiphenylamine (3).⁸

By investigating the influence of the acid strength of various proton donor catalysts on the kinetics of the reaction, Antoni⁸ showed that the reaction rate increases with decreasing pK_a . This explained why several authors^{7, 9, 10} had obtained better yields with *o*-aminophenol hydrochloride (pK_a 4.5) than with catechol (pK_a 9.9); however the yield of phenoxazine did not exceed 30%.

⁷ F. Kehrmann and A. A. Neil, *Ber. Deut. Chem. Ges.* **47**, 3102 (1914).

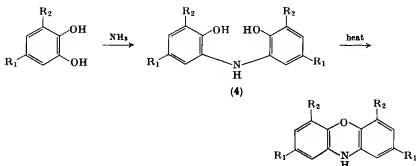
⁸ J. de Antoni, *Compt. Rend.* **252**, 3274 (1961); *Bull. Soc. Chim. France* p. 2871 (1963).

⁹ S. Granik, L. Michaelis, and M. P. Schubert, *J. Am. Chem. Soc.* **62**, 1802 (1940).

¹⁰ H. Gilman and L. O. Moore, *J. Am. Chem. Soc.* **79**, 3485 (1957).

An extension of this synthetic route to alkyl-substituted *o*-aminophenols gave symmetrically substituted dialkyl phenoxazines, but chloro- and methoxy-substituted *o*-aminophenols failed to react under similar conditions. 4-Methyl- (or 4-ethyl-)2-aminophenol, by reaction with the corresponding hydrochloride, yielded 2,8-dimethyl- and 2,8-diethylphenoxazine, respectively.⁸

A better and more recent procedure for the synthesis of unsubstituted phenoxazine involves the autocondensation of *o*-aminophenol



in the presence of iodine, with elimination of ammonia and water. This reaction is also assumed to proceed through an intermediate diphenylamine.^{11, 12}

Sterically hindered catechols, with *tert*-alkyl groups (R₁ and R₂) in the 4- and 6-positions, react with ammonia to yield intermediate 2,2'-dihydroxydiphenylamines (4), which on heating are easily cyclized to the corresponding phenoxazines.¹³

2. The Turpin Reaction

This approach is based on the condensation of *o*-aminophenol with picryl chloride, originally reported by Turpin in 1891.¹⁴ The mechanism consists in an intramolecular nucleophilic displacement of the nitro group from a suitably substituted 2-hydroxy-2'-nitrodiphenylamine (5) by the phenoxide group in alkaline medium.

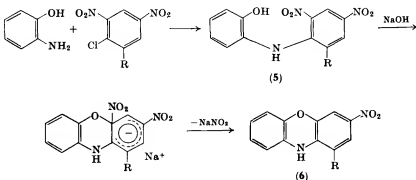
¹¹ P. Müller, N. P. Buu-Hoï, and R. Rips, *J. Org. Chem.* **24**, 37 (1959).

¹² V. G. Samolovova, T. V. Gortinskaya, and M. N. Shchukina, *Zh. Obshch. Khim.* **31**, 1492 (1961).

¹³ K. Ley, *Angew. Chem.* **74**, 871 (1962).

¹⁴ G. S. Turpin, *J. Chem. Soc.* **59**, 714 (1891).

Turpin's reaction has been widely used for preparing substituted phenoxazines.¹⁵⁻²¹ Unsymmetrically substituted halonitrobenzenes which have two nitro groups *ortho* to the reactive halogen produce two isomeric phenoxazines, although usually one isomer predominates.²²



It has been stated^{2, 22-24} that the ring closure of the intermediate diphenylamine derivative (5) does not succeed unless both positions *ortho* to the halogen were substituted, hence that the substituent R in position 6 of the dinitrochlorobenzene (i.e., position 1 of the phenoxazine nucleus) was absolutely necessary. Brady and Waller²⁵ explained this requirement only by steric considerations, as the ring closure could be brought about with widely differing groups in position 6 (NO_2 , SO_3H , COOH , CH_3 , OCH_3). Recently, however, Musso,²⁶ on revising the mechanism of the Turpin reaction on the basis of kinetic measurements, pointed out that the cyclization

¹⁵ B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, pp. 1499, 1504 (1953).

¹⁶ H. G. Garg, *Agra Univ. J. Res. Pt. I* **6**, 11 (1957); *Chem. Abstr.* **52**, 20171 (1958).

¹⁷ A. B. Sen and R. C. Sharma, *J. Indian Chem. Soc.* **34**, 877 (1957).

¹⁸ A. B. Sen and A. K. Roy, *J. Indian Chem. Soc.* **37**, 647 (1960).

¹⁹ J. Ciésłak, S. Kurzepa, and K. Ostalska, *Roczniki Chem.* **34**, 103 (1960).

²⁰ G. E. Bonvicino, L. H. Yagodziniski, and R. A. Hardy, Jr., *J. Org. Chem.* **26**, 2797 (1961).

²¹ H. Musso and P. Wager, *Chem. Ber.* **94**, 2551 (1961).

²² S. P. Gupta and S. S. Joshi, *J. Indian Chem. Soc.* **40**, 400 (1963).

²³ F. Ullmann, *Ann. Chem.* **366**, 79 (1909).

²⁴ F. Ullmann and S. M. Sané, *Ber. Deut. Chem. Ges.* **44**, 3730 (1911).

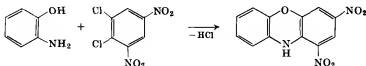
²⁵ O. L. Brady and C. Waller, *J. Chem. Soc.* p. 1218 (1930).

²⁶ H. Musso, *Chem. Ber.* **96**, 1927 (1963).

depends both on the steric and on the electronic nature of the substituent in position 6. Moreover, a new procedure for the Turpin reaction was developed where the sodium salt of the intermediate diphenylamine was isolated and heated in dimethyl sulfoxide or in dimethylformamide, resulting in cyclization to phenoxazines in good yields even with position 6 unsubstituted (**6**, R = H).

3. Cyclization of 2-Chloro-2'-hydroxydiphenylamines

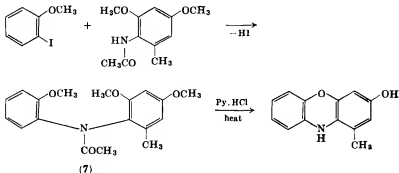
Another way to obtain suitably substituted diphenylamines is the condensation of *o*-aminophenols with activated 1,2-dihalobenzenes.²⁴ The reaction was performed in nonalkaline medium. It is interesting



to note that a Turpin condensation did not take place although the structural requirements for the reaction are fulfilled. This approach may be exemplified by the condensation of *o*-aminophenol with 5,6-dichloro-1,3-dinitrobenzene which yields 1,3-dinitrophenoxazine (**6**, R = NO₂), identical with that obtained by Turpin's reaction with picryl chloride.

4. Cyclization of 2,2'-Dimethoxydiphenylamines

A different phenoxazine ring closure has been effected with 2,2'-dimethoxydiphenylamines.^{21, 27} 2-Acetamido-3,5-dimethoxytoluene



²⁷ H. Beecken and H. Musso, *Chem. Ber.* **94**, 601 (1961).

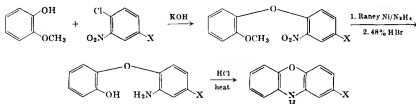
reacts with *o*-iodoanisole in nitrobenzene in the presence of copper powder to give the corresponding 2,2'-dimethoxydiphenylamine (7), which on heating with pyridine hydrochloride is cyclized to 1-methyl-3-hydroxyphenoxazine.

B. RING CLOSURE OF 2,2'-DISUBSTITUTED DIPHENYL ETHERS

The starting substances for the synthesis of the required diphenyl ethers are suitably substituted *o*-nitrochlorobenzenes, which react with phenols containing in the *ortho* position a methoxy, nitro, or halogen group.

1. Cyclization of 2-Amino-2'-hydroxydiphenyl Ethers

The condensation of *o*-nitrochlorobenzenes with *o*-methoxyphenol enables the preparation of phenoxazines substituted in position 2,^{28, 29} which is an important position in connection with biological properties (see Section V, B).



2. Cyclization of 2,2'-Diaminodiphenyl Ethers

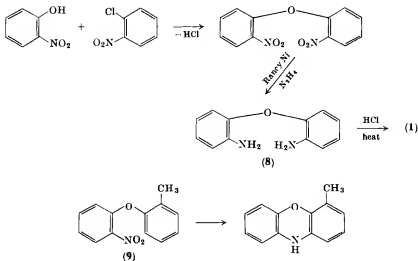
An approach that has been used for the synthesis of unsubstituted phenoxazine in 32% yield involves the condensation of *o*-nitrochlorobenzene with *o*-nitrophenol, followed by reduction and ring closure of the 2,2'-diaminodiphenyl ether (8).^{28, 29}

A similar cyclization occurs also on pyrolysis with a reducing agent (e.g., ferrous oxalate) of the nitroether (9), proceeding through an intermediate monoaminodiphenyl ether.³⁰

²⁸ N. M. Cullinane, H. G. Davey, and H. J. H. Padfield, *J. Chem. Soc.* p. 716 (1934).

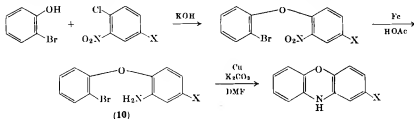
²⁹ M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.* **26**, 1901 (1961).

³⁰ R. Higginbottom and H. Suschitzky, *J. Chem. Soc.* p. 2367 (1962).



3. Cyclization of 2-Amino-2'-bromodiphenyl Ethers

The best general procedure for preparing 2-substituted phenoxazines is the pyrolytic condensation of *o*-chloronitrobenzene derivatives with sodium *o*-bromophenolate,^{20, 29} followed by reduction with stannous chloride or with iron filings in acetic acid and subsequent cyclization of the ether 10. If the ether 10 is previously *N*-formylated,

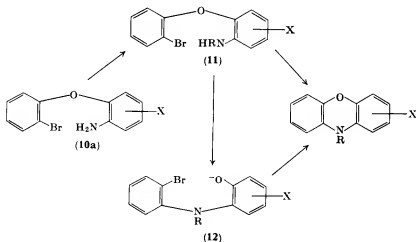


improved yields on cyclization can be realized. *N*-Alkylation of 10a with dialkylaminoalkylhalides in the presence of more than one equivalent of sodamide afforded a mixture of the expected *N*-alkyl derivative (11) and the sodium salt of the isomeric diphenylamine derivative (12).³¹ When only 1 mole of sodamide is employed, solely

³¹ G. E. Bonvicino, L. H. Yagodzinski, and R. A. Hardy, Jr., *J. Org. Chem.* **27**, 4272 (1962).

11 is obtained. The ether **11** on treatment with an excess of sodamide also rearranges to the diphenylamine **12**.

This rearrangement occurs only when a nonpolar solvent, e.g., benzene, is employed, which suggests that the initially formed phenolate salt of **12** is not sufficiently ionized to permit further



reaction of the phenoxide moiety with the *o*-bromine atom. Nevertheless the ring closure of **12** to the corresponding phenoxazine can be performed under conditions similar to those employed with 2-halo-2'-hydroxydiphenylamines (Section II, A, 3). The rearrangement of **11** to **12** in the presence of sodamide and benzene is analogous to the Smiles rearrangement with a halogen as activating group; however, this group must exert its effects through a predominantly inductive mechanism, though in the classical Smiles rearrangement the activation is usually provided by the predominantly resonance effect of an *o*- or *p*-nitro group.

III. Physical Properties

A. GENERAL

The heterocyclic oxygen atom of the phenoxazine nucleus places certain restrictions on the aromaticity of this ring system, which appears to be somewhat less aromatic than the phenazine system, for

instance. The atomic models show that the phenoxazine nucleus is slightly folded along its short axis (i.e., the axis passing through the two central hetero atoms). The dipole moment of phenoxazine, which was found to be 1.93 D (benzene),³² is also consistent with the non-planarity of the molecule. Now, the proton or the substituent at the nitrogen atom may be placed either between or out of the planes of the two lateral rings. Thus, two geometrical configurations can be predicted for the phenoxazine ring, which on analogy to phenothiazine may be called "H-extra" (13a) and "H-intra" (13b) configurations.

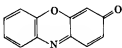


(13a)

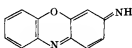


(13b)

There are as yet no reports on the spatial configuration of the phenoxazine nucleus. Such studies have been undertaken, however, for phenoxathiin³³ or phenothiazine,³⁴ and it would be interesting to investigate phenoxazine too, as the energy of the highest occupied molecular orbital is a very sensitive function of the geometrical configuration of the molecule.



(14)



(15)

The phenoxazines are crystalline, colorless to yellow solids, the nitrophenoxazines being colored in different shades of red. It is interesting that phenoxazine and its derivatives do not form hydrochlorides. Most phenoxazines have melting points below 200° and are stable, excepting those substituted in the position *para* to the bridging

³² H. Musso, *Chem. Ber.* **92**, 2881 (1959).

³³ H. Lumbroso and G. Montaudo, *Bull. Soc. Chim. France* p. 2119 (1964).

³⁴ J. P. Malrieu and B. Pullmann, *Theoret. Chim. Acta* **2**, 293 (1964); J. P. Malrieu, *J. Chim. Phys.* **62**, 485 (1965); see also B. Pullmann and A. Pullmann, in "Les Théories Electroniques de la Chimie Organique" p. 446. Masson, Paris, 1952.

nitrogen atom with hydroxy or amino groups which are easily oxidized to 3*H*-phenoxazin-3-ones (14) or 3*H*-phenoxazin-3-imines (15).

Polarographic,³⁵ chromatographic, and electrophoretic³⁶ investigations on phenoxazine derivatives have been reported for naturally occurring phenoxazones (actinomycins).

B. ELECTRONIC ABSORPTION SPECTRA

The ultraviolet spectra of phenoxazine and of several 2-substituted phenoxazines, recorded in Table I, exhibit two bands at 224–247 m μ ($\log \epsilon$ 4.30–4.73) and 318–328 m μ ($\log \epsilon$ 3.84–4.01), while the acetyl-substituted phenoxazines present a third absorption band at about 270 m μ (aromatic ketone band). It can be seen from this table that *N*-alkylation has only a slight influence upon the position and intensity of these bands, and merely produces small bathochromic shifts.

TABLE I

ELECTRONIC SPECTRAL DATA FOR MONOSUBSTITUTED PHENOXAZINES^a

Substituents	λ_{\max} (m μ) ($\log \epsilon$)		
Unsubstituted	239 (4.66)	—	318 (3.93)
2-Chloro	239 (4.73)	—	324 (4.01)
2-Chloro-10-(3'-dimethylaminopropyl)	241 (4.68)	—	328 (3.90)
2-Trifluoromethyl	240 (4.62)	—	318 (3.87)
2-Dimethylsulfonamido	247 (4.69)	—	322 (3.94)
2-Acetyl	224 (4.32)	271 (4.49)	323 (3.84)
2-Acetyl-10-ethyl	227 (4.30)	273 (4.48)	328 (3.95)
3-Acetyl-10-ethyl	261 (4.38)	274 (4.25)	395 (4.11)

^a Data from refs. 20, 29, and 37.

3-Acetyl-10-ethylphenoxazine, however, absorbs at much longer wavelengths than the corresponding 2-acetyl isomer, which allows for easy spectroscopic distinction between these two structures. This effect may be explained by conjugation between the acetyl and NH groups, situated *para* to one another in the 3 isomers.

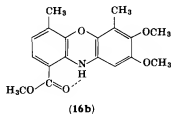
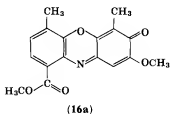
³⁵ M. Fedoronko and H. Berg, *Z. Physik. Chem. (Leipzig)* **220**, 120 (1962).

³⁶ D. M. Schuurmans, D. T. Duncan, and B. H. Olson, *Cancer Res.* **24**, 83 (1964).

C. INFRARED SPECTRA

The infrared spectra of phenoxazine and of a few substituted phenoxazines have been reported,^{29, 37-42} but without a general discussion.

The spectrum of phenoxazine reveals the characteristic absorptions of *ortho*-substituted benzene rings and those of a secondary amino group. All phenoxazines so far investigated show the NH stretching



frequency at $3330\text{--}3413\text{ cm}^{-1}$, the ring stretching modes in the range $1449\text{--}1637\text{ cm}^{-1}$, and the CH out-of-plane bending modes in the region $735\text{--}885\text{ cm}^{-1}$. An examination of the few published spectra dealing with the last region indicates the following ranges: hydrogen atoms in 1-, 2-, 3-, and 4-positions, $735\text{--}765\text{ cm}^{-1}$; hydrogen atoms in 1-, 2-, and 4-positions, $794\text{--}826\text{ cm}^{-1}$ (two adjacent hydrogen atoms) and $858\text{--}885\text{ cm}^{-1}$ (one hydrogen atom).

Substituent vibrations, mostly $\nu\text{ C=O}$ bands in acetyl derivatives, have also been reported.^{40, 43-46} The location of a carbomethoxy group in the vicinity of the nitrogen (i.e., position 9) in compound **16b** has been suggested on the basis of the infrared spectra; the

³⁷ H. Vanderhaeghe, *J. Org. Chem.* **25**, 747 (1960).

³⁸ H. Musso, *Chem. Ber.* **92**, 2862 (1959).

³⁹ H. Musso, *Chem. Ber.* **92**, 2873 (1959).

⁴⁰ G. W. K. Cavill, P. S. Clezy, and F. B. Whitfield, *Tetrahedron* **12**, 139 (1961).

⁴¹ H. Linde, *Arch. Pharm.* **294/66**, 389 (1961).

⁴² H. Linde, *Arch. Pharm.* **295**, 178 (1962).

⁴³ H. Musso and H. G. Matthies, *Chem. Ber.* **90**, 1814 (1957).

⁴⁴ A. Butenandt, E. Biekert, and W. Schäfer, *Ann. Chem.* **632**, 134 (1960).

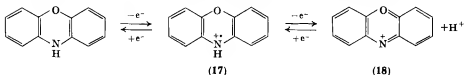
⁴⁵ G. W. K. Cavill, P. S. Clezy, J. R. Tetaz, and R. L. Werner, *Tetrahedron* **5**, 275 (1959).

⁴⁶ H. Musso, *Chem. Ber.* **96**, 1945 (1963).

carbomethoxy C=O stretching band appears shifted from its normal position at 1724 cm⁻¹ in **16a** to 1698 cm⁻¹ in **16b** where an intramolecular hydrogen bond may be formed.⁴⁷

D. ELECTRON SPIN RESONANCE SPECTRA

The electron spin resonance spectra of the positive radical ion formed by phenoxazine in acid solution have been reported by Tuck and Schieser.⁴⁸ This radical is similar in structure to the free radical ion formed with anthracene (which, however, is strictly planar), but it is considerably more stable, owing to the greater possibilities of resonance due to the presence of nitrogen in the central ring. For this



radical, the authors postulate the structure of a semiquinone-type ion (17), an intermediate state between the phenoxazine and the phenoxazonium ion (18); it could be demonstrated that the ring nitrogen of the free radical (17) was protonated.

The phenoxazine radical ion was obtained in concentrated sulfuric acid with 30% hydrogen peroxide. However, phenoxazine dissolved in sulfuric acid on standing for a few days yielded an identical spectrum without addition of any oxidant.

The radical ion of phenoxazine has a uniformly spaced four-line spectra with the line intensities in the ratio 1:2:2:1. The measured coupling constant was 9.83 gauss, the line width 8.19 gauss, and the g value 2.0049. This hyperfine structure can be interpreted as a basic three-line splitting by the nitrogen-14 nucleus (nuclear spin 1) and a doublet splitting with nearly identical spacing due to the attached acidic proton (nuclear spin $\frac{1}{2}$).

A number of ESR spectra of semiquinone radicals, formed as intermediate reduction products of phenoxazine dyestuffs, have been investigated by Heineken and Bruin in acid and in alkaline solution.^{49, 50}

⁴⁷ H. Brockmann, *Fortschr. Chem. Org. Naturstoffe* **18**, 1 (1960).

⁴⁸ L. D. Tuck and D. W. Schiesler, *J. Phys. Chem.* **66**, 937 (1962).

⁴⁹ F. W. Heineken, M. Bruin, and F. Bruin, *J. Chem. Phys.*, **37**, 1479 (1962).

⁵⁰ M. Bruin, F. Bruin, and F. W. Heineken, *J. Org. Chem.*, **29**, 507 (1964).

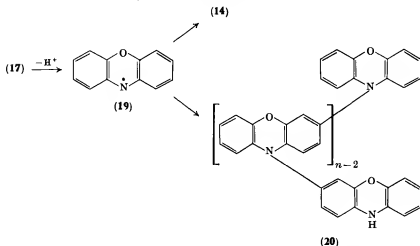
Lagerkrantz and Yhland⁵¹ could show that some phenoxazine dyes have an ESR absorption in the solid state even without any oxidant added. In acid solution with relatively high concentration these dyes produce a spectrum of four lines, with the line width of 7.6 gauss whereas the spectrum in alkaline solution where no protonation of the ring nitrogen occurs consists of only three lines with relative intensities of 1:1:1; the separation between these lines is 7.7 gauss. When using less concentrated solutions the three- and four-line spectra can be resolved into a more complicated hyperfine pattern, due to the ring protons.

A number of oxazine dye salts, on dissolving in aqueous alkali, precipitated the free radical; thus the dye Meldola's blue, which precipitates even in almost neutral solution, yields a very stable solid free radical which can be kept in air and can be used as standard like 2,2-diphenyl-1-picrylhydrazyl.

IV. Chemical Properties

A. OXIDATION

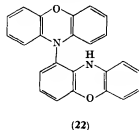
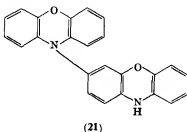
Phenoxazines are known to be readily oxidized. According to Musso³⁸ the first stage in the oxidation of phenoxazine with ferric



chloride, potassium nitrosodisulfonate, bromine, potassium permanganate, and other oxidizing agents is the red-violet phenox-

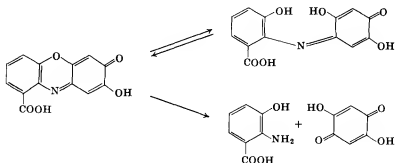
⁵¹ C. Lagercrantz and M. Yhland, *Acta Chem. Scand.* **15**, 1204 (1961).

azinyl radical cation **17**. This radical cation is characterized by a very strong absorption at 530–535 $m\mu$ which makes it suitable for kinetic measurements (see Section V, C). In neutral or alkaline solution **17** splits off a proton to give the nitrogen radical **19** which either polymerizes to yield polyphenoxazines (**20**) or is converted into 3*H*-phenoxazin-3-one (**14**), the ratio of the two products depending on the



acidity of the solution. With decreasing pH, the phenoxazone yield increases appreciably and that of polyphenoxazine decreases.

Attempts to isolate *N,N'*-diphenoxazine did not succeed.³² In the polymers (**20**) the phenoxazinyl residues are linked together so that



positions 3 and 10 are linked to one another. The potassium salt of phenoxazine, on boiling with bromine, however, afforded two *N,C*-biphenoxazines (**21** and **22**); the latter results also on refluxing phenoxazine with potassium in xylene, without addition of bromine, but in the presence of air.³⁹

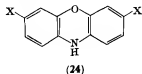
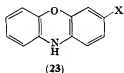
Phenoxazine and 3-acetoxypheinoxazine, as well as their 10-acetyl derivatives, when oxidized with nitrous acid at 5°, are converted into 3*H*-phenoxazin-3-ones.⁴⁰

With the 3*H*-phenoxazin-3-one system ring opening may occur; the phenoxazine molecule is split by dilute alkali at the oxygen bridge with formation of the phenylquinone-imine system, a reversible reaction, whereas by concentrated alkali at 70° both the oxygen and nitrogen bridges are irreversibly cleaved.⁵²

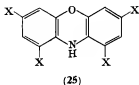
B. ELECTROPHILIC AROMATIC SUBSTITUTION

1. Halogenation

a. *Bromination.* Kehrman⁵³ first treated phenoxazine in benzene with bromine to obtain a deep violet solution and a nearly black unidentified precipitate. Musso,³⁸ reinvestigating this work, was able to isolate both 3-bromophenoxazine (**23**, X = Br) and 3,7-dibromophenoxazine (**24**, X = Br) from the precipitate. On bromination in



various solvents, green-brown colored by-products always resulted, which proved to be mixtures of brominated polyphenoxazines; this shows that along with the bromination a partial oxidation and polymerization of phenoxazine takes place.



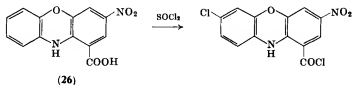
Bromination of *N*-acetylphenoxazine in acetic acid yielded, besides **23** (X = Br) and **24** (X = Br), a small amount of 1,3,7,9-tetrabromophenoxazine (**25**, X = Br), which could be readily isolated because of its low solubility. The monobromo- and dibromophenoxazines easily give *N*-acetyl derivatives, but the tetrabromophenoxazine, the corresponding tetranitrophenoxazine (**25**, X = NO₂), and other phenox-

⁵² A. Butenandt, J. Keck, and G. Neubert, *Ann. Chem.* **602**, 61 (1957).

⁵³ F. Kehrman, *Ann. Chem.* **322**, 1 (1902).

azines with a nitro group in the vicinity of the nitrogen (i.e., position 1 and/or 9) could not be acetylated, even under forcing conditions.⁵⁴ *N*-Substituted 1,3-dinitrophenoxazines, however, have been obtained by a Turpin ring closure.⁵⁵

b. *Chlorination*. The only chlorination of phenoxazine so far reported occurs on reaction with thionyl chloride. Predvoditeleva



and Shehukina⁵⁶ found that unsubstituted phenoxazine gave 1,3,7,9-tetrachlorophenoxazine (**25**, X=Cl); no monochloro- or dichlorophenoxazine could be isolated during this reaction. However, with 3-nitrophenoxazine-1-carboxylic acid (**26**) under similar conditions, chlorination occurs only in the position *para* to the nitrogen; the carboxyl group is converted simultaneously into the corresponding acid chloride.

2. Nitration

Phenoxazine itself reacts very violently even with dilute nitric acid to give tetranitrophenoxazine (**25**, X=NO₂) and no mono or dinitro derivatives.⁵⁴ *N*-Acetylphenoxazine, however, is nitrated in acetic acid to give a mononitro-*N*-acetylphenoxazine,²⁶ which after deacetylation proved to be identical with 3-nitrophenoxazine (**23**, X=NO₂), obtained by the Turpin reaction (see Section II, A, 2). On nitration in acetic anhydride *N*-acetylphenoxazine yielded a mixture of **25** (X=NO₂) and the acetyl derivative of **24** (X=NO₂).

The positions of the nitro groups have been demonstrated also by the fact that both 1,3-dinitro- and 1,3,7-trinitrophenoxazine, obtained by Turpin's reaction, are further nitrated to the same 1,3,7,9-tetranitrophenoxazine.⁵⁷

⁵⁴ F. Kehrman and A. Saager, *Ber. Deut. Chem. Ges.* **36**, 475 (1903).

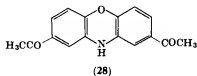
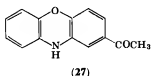
⁵⁵ H. Linde, *Arch. Pharm.* **294/66**, 57 (1961).

⁵⁶ G. S. Predvoditeleva and M. N. Shehukina, *Zh. Obshch. Khim.* **30**, 1893 (1960).

⁵⁷ E. Misslin and A. Ban, *Helv. Chim. Acta* **2**, 285 (1919).

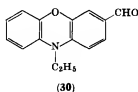
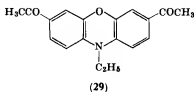
3. Friedel-Crafts Reactions on Phenoxazines

Friedel-Crafts substitution of phenoxazine or *N*-acetylphenoxazine with acetyl chloride in the presence of aluminum chloride was found to give a *C*-monoacetylphenoxazine.^{11, 58} This acetylphenoxazine, which was first formulated as 3-acetylphenoxazine,¹¹ was shown later by Vanderhaeghe⁵⁷ to be 2-acetylphenoxazine (**27**); this conclusion was supported also by the examination of the infrared and ultraviolet



spectra of both 2-acetyl- and 3-acetyl-10-ethylphenoxazine (the latter was synthesized for comparison by another method).

Similarly, 2-chloroacetylphenoxazine, 2-propionylphenoxazine, and 2-butyrylphenoxazine have been obtained by Friedel-Crafts condensation of phenoxazine with the proper acyl halides.⁵⁸⁻⁶⁰



Friedel-Crafts reaction of *N*-acetylphenoxazine in carbon disulfide with a large excess of acetyl chloride and aluminum chloride yielded 2,8-diacetylphenoxazine (**28**), which proved to be identical with the diacetylphenoxazine which was formed by oxidation of 2,8-diethylphenoxazine with potassium permanganate (see Section IV, E).⁶¹

The product obtained by Friedel-Crafts acetylation of 10-ethylphenoxazine, however, was shown to be 3,7-diacetyl-10-ethylphenoxazine (**29**) and not a 2,8-diacetyl derivative, the assignment

⁵⁸ Recherche et Industrie Thérapeutiques (R.I.T.), Belgian Patent 575, 133 (1959); *Chem. Abstr.* **54**, 5708 (1960).

⁵⁹ H. Vanderhaeghe, M. Claesen, and P. Kolosy, *Congr. Sci. Pharm.*, **21**^o, Pisa, Conf. Commun., 1961 p. 907 (1961); *Chem. Abstr.* **59**, 6391 (1963).

⁶⁰ G. S. Predvoditeleva and M. N. Shchukina, *Zh. Obshch. Khim.* **31**, 1497 (1961).

⁶¹ J. de Antoni, *Bull. Soc. Chim. France* p. 2874 (1963).

of this structure being supported by the infrared and ultraviolet spectra.³⁷

It follows that the phenoxazine ring system possesses two activating and competing hetero atoms which may direct the substitution. With phenoxazine itself acetylation first gives the *N*-acyl derivative, in which the amino group is deactivated, and substitution in the Friedel-Crafts reaction occurs *para* to the oxygen atom (i.e., 2- and/or 8-positions). If *N*-acylation is prevented, as in *N*-alkylphenoxazines, the acyl groups are directed *para* to the nitrogen function owing to the stronger orienting influence of the amino group in this case.

4. The Vilsmeier-Haack Reaction

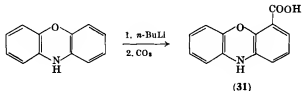
10-Ethylphenoxazine reacts with *N*-methylformanilide in the presence of phosphorus oxychloride in *o*-dichlorobenzene to give 3-formyl-10-ethylphenoxazine.³⁷ The formyl group enters *para* to the nitrogen atom as in the Friedel-Crafts reaction with 10-ethylphenoxazine (30).

From the available data we may conclude that the reactivity of the carbon atoms of the phenoxazine ring during electrophilic substitution decreases in the following order 3(7):1(9):2(8):4(6).

C. NUCLEOPHILIC SUBSTITUTION

Metalation of Phenoxazine

Phenoxazine, as well as its *N*-alkyl and *N*-aryl derivatives, are metalated slowly by *n*-butyllithium in ether; in each case some dimetalation also occurs. The metalation of the unsubstituted phenoxazine followed by carbonation gives phenoxazine-4-carboxylic acid (31).



The position of metalation adjacent to the oxygen atom (i.e., in position 4) was assigned by Gilman and Moore⁶² on chemical grounds and supported by the infrared spectra; this resembles the metalation

⁶² H. Gilman and L. O. Moore, *J. Am. Chem. Soc.* **80**, 2195 (1958).

of phenoxathiin,⁶³ but differs from that of phenothiazine, where metalation occurs primarily in the 1-position, adjacent to the nitrogen.⁶⁴

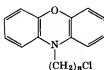
D. N-SUBSTITUTION

A large amount of work has been carried out in this direction, because of the biological interest shown by the products.

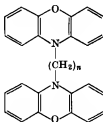
1. Alkylation

Phenoxazine resists alkylation with alkyl halides, because the nitrogen atom of the phenoxazine nucleus is not sufficiently basic for direct action. *N*-Alkylation can be achieved, however, in the presence of basic condensing agents like sodamide.

a. *With Alkyl Halides.* The general procedure for preparing *N*-alkyl derivatives consists in the condensation of phenoxazines with the requisite alkyl halide or with a dialkylaminoalkyl chloride in the



(32)



(33)

presence of sodamide, either in liquid ammonia or in anhydrous solvents such as toluene or benzene.^{10, 19, 29, 65-70} The reaction of phenoxazine with mixed chlorobromoalkanes in the presence of

⁶³ H. Gilman, M. W. Van Ess, H. B. Willis, and C. G. Stuckwisch, *J. Am. Chem. Soc.* **62**, 2606 (1940).

⁶⁴ H. Gilman, D. A. Shirley, and P. R. Van Ess, *J. Am. Chem. Soc.* **66**, 625 (1944).

⁶⁵ G. Frangatos, G. Kohan, and F. L. Chubb, *Can. J. Chem.* **38**, 1021 (1960).

⁶⁶ H. Linde, *Arch. Pharm.* **293/65**, 537 (1960).

⁶⁷ H. J. Conrad and H. Linde, *Arch. Pharm.* **294/66**, 45 (1961).

⁶⁸ H. Vanderhaeghe and L. Verlooy, *J. Org. Chem.* **26**, 3827 (1961).

⁶⁹ K. Stach, M. Thiel, and F. Bickelhaupt, *Monatsh. Chem.* **93**, 1090 (1962).

⁷⁰ F. Sparatore and V. Boido, *Ann. Chim. (Rome)* **54**, 591 (1964).

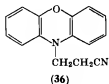
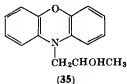
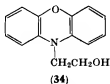
sodamide gave reactive *N*-chloroalkylphenoxazines (32),^{68, 71} whereas the reaction with α,ω -dibromoalkyl halides furnished α,ω -diphenoxazinylalkylenes (33).⁶⁷

This general procedure for preparing *N*-alkylphenoxazine derivatives was not successful in the case of methyl phenoxazine-4-carboxylate, where sodamide reacts with the substituent.⁶²

A modification of this method involves the treatment of phenoxazine with the corresponding alkyl halide in the presence of powdered sodium hydroxide, to give the *N*-alkylphenoxazines.^{72, 73} Phenoxazine and *n*-butyllithium in pentane-heptane under a nitrogen atmosphere yielded *N*-lithiophenoxazine, a yellow-red precipitate, which on refluxing with the appropriate alkyl halides gave *N*-alkylphenoxazines.⁷⁴

10-Arylphenoxazines have been obtained similarly with aryl halides in the presence of sodamide,⁶⁷ or on heating phenoxazine and an aryl iodide or aryl bromide with anhydrous potassium carbonate and a small amount of copper bronze as catalyst.¹⁰

b. *With 1,2- and 1,3-Epoxydes.* *N*- β -Hydroxyalkyl derivatives can be obtained by the reaction of phenoxazine with epoxides. Phenoxazine was condensed with ethylene oxide and with propylene oxide in toluene solution in the presence of sodamide to give 10-(2'-hydroxyethyl)phenoxazine (34) and 10-(2'-hydroxypropyl)phenoxazine (35), respectively.^{10, 66, 73}



c. *Cyanoethylation.* It has been shown that phenoxazine undergoes smooth β -cyanoethylation with acrylonitrile in the presence of benzyltrimethylammonium methoxide to give 10-(2'-cyanoethyl)phenoxazine (36), the reaction being even more vigorous than in the

⁷¹ A. E. Gal and S. Avakian, *J. Med. Pharm. Chem.* **6**, 809 (1963).

⁷² V. G. Samolovova, T. V. Gortinskaya, and M. N. Shehukina, *Zh. Obshch. Khim.* **30**, 1516 (1960).

⁷³ V. G. Samolovova, T. V. Gortinskaya, and M. N. Shehukina, *Zh. Obshch. Khim.* **32**, 1085 (1962).

⁷⁴ D. A. Shirley, K. Sen, and J. C. Gilmer, *J. Org. Chem.* **26**, 3587 (1961).

case of phenothiazine, probably because of the higher solubility of phenoxazine in acrylonitrile.^{65,72,75} Under similar or even more drastic conditions α -methylacrylonitrile failed to undergo condensation. The *N*-cyanoethylphenoxazine was hydrogenated in aqueous ammonia over Raney nickel to 10-(3'-aminopropyl)phenoxazine, while on treatment with concentrated sulfuric acid it gave 3-(10-phenoxazinyl)propionamide, which on further hydrolysis yielded the corresponding propionic acid.

A number of simple *N*-alkylphenoxazines are recorded in Table II.

TABLE II
N-SUBSTITUTED PHENOXAZINES

Alkyl			Acyl		
Substituent	M.p. (°C)	Ref.	Substituent	M.p. (°C)	Ref.
CH ₃	35-37	10	COCl	142-144	71, 73, 76
CH ₂ CH ₃	46-47	10	COCH ₃	142	28
CH ₂ CH ₂ Cl	62	74	COCH ₂ Cl	145-146.5	12, 71
CH ₂ CH ₂ OH	109-110	66, 73	COCH(CH ₃)Cl	131-132	71
CH ₂ CH ₂ CN	123-124	65, 72, 75	COOCH ₃	119-120	73
CH ₂ CH ₂ CH ₂ Cl	54-55	68, 71	COOC ₂ H ₅	74-75	71
CH ₂ CH ₂ CH ₂ Br	55-56	65	CONHNH ₂	156-157	71, 77
CH ₂ CH ₂ CH ₂ OH	68	65	COCH(C ₆ H ₅) ₂	124-125	77
CH ₂ CHOHCH ₃	95-98	68			
CH ₂ CH ₂ CH ₂ NH ₂	63-64	72			
CH ₂ CH ₂ CONH ₂	173-174	72			
CH ₂ CH ₂ COOH	138-139	65, 72, 75			
CH ₂ C ₆ H ₅	127-128	10			

2. Acylation

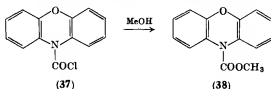
Phenoxazine is easily acylated with acetic anhydride or on heating with acyl chlorides in benzene.^{12,71,75} A very convenient method is the reaction of phenoxazine with phosgene to give phenoxazine-10-carbonyl chloride (37).^{73,76} This acyl chloride is very stable; it is not decomposed by short boiling in water or methanol, and gives phenoxazine only with hot sodium hydroxide. On prolonged boiling

⁷⁵ P. Müller, N. P. Buu-Hoï, and R. Rips, *J. Org. Chem.* **24**, 1699 (1959).

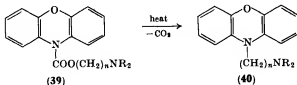
⁷⁶ M. Claesen and H. Vanderhaeghe, *J. Org. Chem.* **26**, 4130 (1961).

with methanol the corresponding ester (38) was obtained, which resulted also on treating phenoxazine in methanol with methyl chloroformate.⁷³ Other simple *N*-acylphenoxazines are collected in Table II.

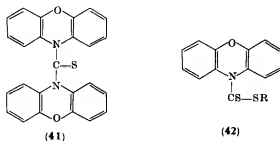
Various dialkylaminoalkyl esters of phenoxazine-10-carboxylic acid (39) have been prepared by reacting the acid chloride 37 with an



appropriate amino alcohol; on heating under reduced pressure these esters undergo a carbon dioxide elimination which has proved useful for the preparation of the corresponding dialkylaminoalkylphenoxazines (40).⁷⁶



The condensation of phenoxazine in refluxing benzene with thiophosgene, in order to obtain the 10-thiocarbonyl chloride, gave only a black unidentified precipitate, while the filtrate yielded a yellow compound to which structure 41 was assigned.⁷⁷ Phenoxazine treated

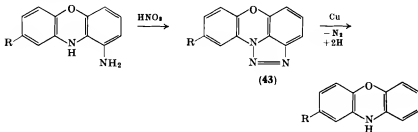


⁷⁷ V. G. Samolovova, T. V. Gortinskaya, and M. V. Shechukina, *Zh. Obshch. Khim.* **34**, 3791 (1964).

with phenyllithium and carbon disulfide in ether gave the *N*-dithiocarboxylate, which on heating with dialkylaminoalkyl chlorides afforded the corresponding dithioesters (42), useful as spasmolytics.⁷⁸ *N*-Sulfonyl derivatives, prepared in pyridine solution, have also been reported.⁷⁷

E. OTHER REACTIONS WITH PHENOXAZINE DERIVATIVES

Most aminophenoxazines have been obtained by stannous chloride or catalytic reduction of the corresponding nitro compounds, readily available by Turpin's reaction.^{15, 17, 18, 79, 80} 1-Nitrophenoxazine, on



reduction with stannous chloride, yields 1-aminophenoxazine, which in turn with sodium nitrite in sulfuric acid is converted into compound 43, with three nitrogen atoms forming a triazole ring. This on boiling with copper in ethanolic sulfuric acid undergoes reduction and elimination of nitrogen.¹⁹ This sequence of reactions provides a convenient way of eliminating the 1-nitro group.

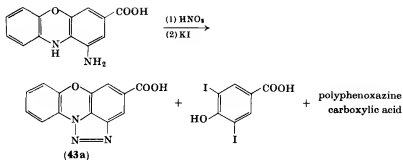
Diazotization of 1-aminophenoxazine-3-carboxylic acid followed by treatment with potassium iodide did not yield the expected iodophenoxazine, but did yield the triazolo derivative (43a), along with polyphenoxazinecarboxylic acid and 3,5-diiodo-4-hydroxybenzoic acid; the latter was considered by Linde⁴¹ as a cleavage product of the phenoxazine nucleus and its appearance must be connected with the presence of the 3-carboxylic group, because with other groups no such cleavage occurs.⁴²

Reductive acetylation of various 3*H*-phenoxazin-3-ones has been shown to yield the corresponding 3-acetoxypheinoxazines.⁴⁰

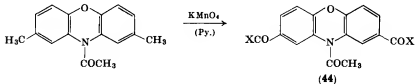
⁷⁸ Société des Usines Chimiques Rhône-Poulenc, French Patent 1,173,149 (1959); *Chem. Abstr.* **56**, 3488 (1962).

⁷⁹ F. Kehrmann and L. Löwy, *Ber. Deut. Chem. Ges.* **44**, 3006 (1911).

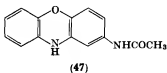
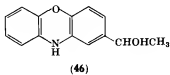
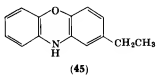
⁸⁰ A. B. Sen and R. C. Sharma, *J. Indian Chem. Soc.* **33**, 671 (1956).



Further reactions are provided by the mild oxidation of the methyl groups in 2,8-dimethylphenoxazine (protected by *N*-acetylation) which yields *N*-acetylphenoxazine-2,8-dicarboxylic acid (**44**, X = OH), from which various functional derivatives have been prepared (**44**, X = Cl, NH₂, OR, NR₂).^{61, 81}



A similar oxidation of 2,8-diethylphenoxazine yields 2,8-diacetylphenoxazine,^{61, 82} identical with that obtained by Friedel-Crafts substitution (Section IV, B, 3).

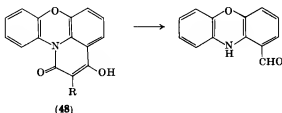


⁸¹ R. Hazard, J. Cheymol, P. Chabrier, A. Sekera, and J. de Antoni, *Compt. Rend.* **252**, 4166 (1961).

⁸² R. Hazard, J. Cheymol, P. Chabrier, A. Sekera, and J. de Antoni, *Compt. Rend.* **253**, 1263 (1961).

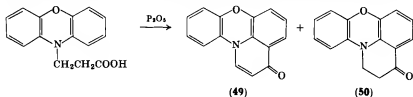
2-Acetylphenoxazine, readily obtainable by a Friedel-Crafts reaction, affords 2-ethylphenoxazine (45) on Wolff-Kishner reduction; reduction with sodium borohydride gives 1-(2-phenoxazinyl)ethanol (46) and the Schmidt reaction yields 2-acetylaminophenoxazine (47).^{37, 83}

The condensation of phenoxazine with diethylalkylmalonates at elevated temperatures in the presence of a silicate catalyst has been



found to give pyridophenoxazines (48),⁸⁴ which after a sequence of transformations yield phenoxazine-1-aldehyde.^{85, 86} This constitutes the only way so far reported of introducing an aldehyde group into position 1 of the phenoxazine ring.

3-(10-Phenoxazinyl)propionic acid undergoes an interesting cyclization with phosphorus pentoxide, to give a mixture of the pyridophenoxazine (49) and the corresponding dihydroderivative (50).^{65, 75}



V. Biologically Important Phenoxazines and Industrial Uses

A. NATURALLY OCCURRING PHENOXAZINES

Recent investigations have shown the existence of a number of phenoxazine derivatives in nature, which, with a few exceptions only,

⁸³ G. S. Predvoditeleva and M. N. Shehukina, *Zh. Obshch. Khim.* **32**, 113 (1962).

⁸⁴ M. Harfenist, R. Blumfeld, T. Capiris, and E. Magnien, *J. Org. Chem.* **27**, 3977 (1962).

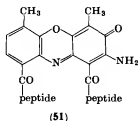
⁸⁵ M. Harfenist, *J. Org. Chem.* **27**, 4326 (1962).

⁸⁶ M. Harfenist (Burroughs Wellcome & Co.), British Patent 983,600 (1965); *Chem. Abstr.* **63**, 615 (1965).

occur in the oxidized state, mainly as derivatives of 2-amino-3*H*-phenoxazin-3-ones.

1. Actinomycins

The actinomycins represent a group of closely related, very toxic antibiotics produced by certain species of *Streptomyces*. Actinomycin A which was discovered in 1940 by Waksman and Woodruff⁸⁷ was



the first antibiotic obtained crystalline from a microorganism. Subsequent research work has recognized the "chromopeptide" structure of these antibiotics, based on structure 51.

Eighteen different actinomycins have been described, differing in the amino acid sequence in the peptide chains and the total synthesis of some have been reported.⁸⁸ Much of our knowledge of this class is due to the work of Brockmann, who has published comprehensive reviews.^{47, 89} Recently Weinstein *et al.*⁹⁰ reported the synthesis of simple actinomycin analogs, which might yield effective antibacterial compounds or antitumor agents less toxic than the natural actinomycins.

2. Questioniomycin A (2-Amino-3*H*-phenoxazin-3-one)

A number of enzymes, isolated from mammalian tissues,⁹¹ from cell-free extracts of *Streptomyces antibioticus*,⁹² and from the leaves of

⁸⁷ S. A. Waksman and H. B. Woodruff, *Proc. Soc. Exptl. Biol. Med.* **45**, 609 (1940); *Chem. Abstr.* **35**, 1081 (1941).

⁸⁸ H. Brockmann and H. Lackner, *Naturwissenschaften* **47**, 230 (1960); **51**, 384 (1964).

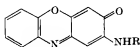
⁸⁹ H. Brockmann, *Angew. Chem.* **72**, 939 (1960).

⁹⁰ B. Weinstein, O. P. Crews, M. A. Leaffer, B. R. Baker, and L. Goodman, *J. Org. Chem.* **27**, 1389 (1962).

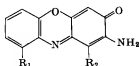
⁹¹ H. R. Gutmann and H. T. Nagasawa, *J. Biol. Chem.* **234**, 1593 (1959).

⁹² E. Katz and H. Weissbach, *J. Biol. Chem.* **237**, 882 (1962).

Tecoma stans,⁹³ have been shown to catalyze the condensation of *o*-aminophenol to 2-amino-3*H*-phenoxazin-3-one (**52**, R = H) to which the name *questiomycin A* has been given by Anzai *et al.*⁹⁴ This compound has been isolated also from *Streptomyces fungicidicus*,⁹⁵ and, along with 2-acetyl-amino-3*H*-phenoxazin-3-one (**52**, R = COCH₃), from members of the actinomycete genus *Waksmania*.⁹⁶



(52)

(53a) R₁ = CH₂OH, R₂ = COOH(53b) R₁ = R₂ = COOH(53c) R₁ = COOH, R₂ = CHO

3. Fungal Metabolites

Three fungal metabolites containing the oxidized phenoxazine system have been isolated from various wood-rotting fungi. The constitution of these coloring substances from mushrooms has been established independently by Gripenberg⁹⁷ and Cavill and co-workers^{40, 45} as possessing the following structures: cinnabarin (= polystictin) (**53a**), cinnabarinic acid (**53b**), and tramesanguin (**53c**).

4. Ommochromes

This name was given to a class of acidic pigments which occur mainly as eye-coloring substances in different arthropods and are located in the ommatides of the insect eye. Through the work of Butenandt and co-workers⁹⁸ the structure of the following three ommochromes has been established: xanthommatin (**54**), rhodommatin (**55a**), and ommatin D (**55b**).

⁹³ P. M. Nair and C. S. Vaidyanathan, *Biochim. Biophys. Acta* **81**, 507 (1964).

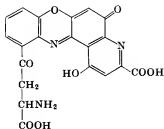
⁹⁴ K. Anzai, K. Isono, K. Okuma, and S. Suzuki, *Rika Gaku Kenkyusho Hokoku* **36**, 577 (1960); *Chem. Abstr.* **55**, 25150 (1961); *J. Antibiotics (Tokyo) Ser. A* **13**, 125 (1960).

⁹⁵ M. Matsuoka, *J. Antibiotics (Tokyo) Ser. A* **13**, 121 (1960).

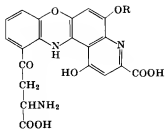
⁹⁶ N. N. Gerber and M. P. Lechevalier, *Biochemistry* **3**, 598 (1964).

⁹⁷ J. Gripenberg, *Acta Chem. Scand.* **12**, 603 (1958); **17**, 703 (1963).

⁹⁸ A. Butenandt and W. Schäfer, in "Recent Progress in the Chemistry of Natural and Synthetic Coloring Matters" (T. S. Gore, B. S. Joshi, S. V. Sunthakar, and B. D. Tilak, eds.), p. 13, Academic Press, New York, 1962.



(54)

(55a) R = β -glucose(55b) R = SO₃H

B. BIOLOGICAL ACTIVITY

Compounds of pharmacological interest have been found among phenoxazine derivatives, including various analogs of phenothiazine, which often are less toxic than the latter.⁹⁹ For the biologically active phenoxazines the general structural formula **56** can be forwarded, where X may be hydrogen, halogen, methyl, methoxyl, acyl, cyano, or trifluoromethyl and Y a dialkylamino-substituted alkyl side chain.

Pharmacological tests have shown that the substituent in position 2 produces an exaltation of the pharmacodynamic activity. These compounds have been claimed to be nervous system depressants, in particular with sedative, antiepileptic, and tranquilizing activity.¹⁰⁰⁻¹⁰⁵ Spasmolytic activity was shown by phenoxazine-10-carboxylic¹⁰⁶ or phenoxazine-10-dithiocarboxylic alkylamino esters,⁷⁸

⁹⁹ U. Hörlein, K. H. Risse, and W. Wirth, *Med. Chem. Abhandl. Med.-Chem. Forschungsstaetten Farbenfabriken Bayer* **7**, 79 (1963); *Chem. Abstr.* **61**, 1128 (1964).

¹⁰⁰ C. F. Boehringer & Soehne, G.m.b.H., Belgian Patents 631,122 and 631,192 (1963); *Chem. Abstr.* **60**, 14514 (1964).

¹⁰¹ Smith, Kline & French Lab., British Patent 897,158 (1962); *Chem. Abstr.* **57**, 12506 (1962).

¹⁰² M. P. Olmsted (Smith, Kline & French Lab.), U.S. Patent 2,947,746 (1960); *Chem. Abstr.* **55**, 11443 (1961).

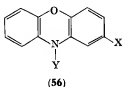
¹⁰³ Société des Usines Chimiques Rhône-Poulenc, French Patent 1,169,518 (1958); *Chem. Abstr.* **55**, 3628 (1961).

¹⁰⁴ P. N. Craig (Smith, Kline & French Lab.), U.S. Patents 2,947,747 and 2,947,745 (1960); *Chem. Abstr.* **55**, 580 and 582 (1961).

¹⁰⁵ A. Ribbentrop and W. Schaumann, *Arch. Intern. Pharmacodyn.* **149**, 374 (1964); *Chem. Abstr.* **61**, 9924 (1964).

¹⁰⁶ A. Sekera, *J. Mondial Pharm.* **5**, 5 (1962); *Chem. Abstr.* **58**, 4421 (1963).

and antitubercular activity by several 2,7-bisalkylamino-3*H*-phenoxazin-3-imines.¹⁰⁷ Rogers *et al.*¹⁰⁸ have published a study on the anthelmintic properties of unsubstituted phenoxazine, which shows a similar activity to that of phenothiazine, whereas 2,4,6,8-tetra-*tert*-butylphenoxazine has been found to be a parasiticide and herbicide.¹⁰⁹



C. PRACTICAL APPLICATIONS

Besides potential pharmacological applications, a number of other uses have been described for phenoxazine derivatives. The semi-quinone radical obtained on oxidation of phenoxazine with various oxidants, which has been shown to give a characteristic absorption at about 530 $m\mu$, was used by Sawicki *et al.*¹¹⁰ in a new method for the spectrophotometric determination of nitrite; the aqueous nitrite sample is treated with a 0.1% solution of phenoxazine in glacial acetic acid and the absorbance is read at 530 $m\mu$.

The change in color from various shades of red to yellow, which accompanies the reduction of substituted 3*H*-phenoxazin-3-ones, has made them suitable as bromometric and stannometric redox indicators¹¹¹⁻¹¹³; Ružička¹¹⁴ reported also the microdetermination of compounds containing SH groups with such derivatives. Phenoxazine has been described as a stabilizer for polymerizable vinylpyridines¹¹⁵

¹⁰⁷ A. Girard (Russel-UCLAF, S.A.), U.S. Patent 3,048,586 (1962); *Chem. Abstr.* **58**, 1471 (1963).

¹⁰⁸ W. P. Rogers, J. Cymerman-Craig, and G. P. Warwick, *Brit. J. Pharmacol.* **10**, 340 (1955).

¹⁰⁹ H. B. Rickert and W. M. Geiger (Dow Chemical Co.), U.S. Patent 2,945,856 (1960); *Chem. Abstr.* **54**, 24819 (1960).

¹¹⁰ E. Sawicki, T. W. Stanley, J. Pfaff, and H. Johnson, *Anal. Chem.* **35**, 2183 (1963).

¹¹¹ E. Ružička, *Collection Czech. Chem. Commun.* **24**, 930 (1959).

¹¹² E. Ružička, *Collection Czech. Chem. Commun.* **29**, 2244 (1964).

¹¹³ S. Musha and T. Kitagawa, *Nippon Kagaku Zasshi* **76**, 1289 (1955); *Chem. Abstr.* **51**, 12737 (1957).

¹¹⁴ E. Ružička, *Chem. Listy* **51**, 969 (1957); *Chem. Abstr.* **51**, 11936 (1957).

¹¹⁵ A. M. Snitzer and R. E. Reusser (Phillips Petroleum Co.), U.S. Patent 2,857,389 (1958); *Chem. Abstr.* **53**, 6296 (1959).

and for polyolefins¹¹⁶ (polyethylene and polystyrene). Benevolenskii and Zhuravlev¹¹⁷ reported the radioprotective and antioxidative action of a number of phenoxazine derivatives.

Mention should be made of oxazine dyes, used also as biological stains, which are oxidized phenoxazine derivatives containing suitable auxochromic groups. A detailed treatment of these dyes, however, is beyond the scope of this review. Most of the industrial phenoxazine dyes are derived from benzophenoxazines (e.g., Meldola's blue) or from more complex ring systems containing the phenoxazine residue (triphenyldioxazine dyes).^{3,118} The long-known dyestuffs orcein and litmus which are prepared by the action of ammonia on certain lichens, and may also occur accidentally in nature, are both based on the oxidized phenoxazine ring system as shown by Musso and co-workers.¹¹⁹

ACKNOWLEDGMENT

The authors are indebted to Dr. A. T. Balaban for critically reading the paper.

¹¹⁶ K. Peterlein and K. Schmitz (Gelsenberg Benzin Akt. Ges.), German Patent 1,103,577 (1961); *Chem. Abstr.* **55**, 27980 (1961).

¹¹⁷ V. N. Benevolenskii and A. I. Zhuravlev, *Radiobiologiya* **3**, 745 (1963); *Chem. Abstr.* **60**, 836 (1964).

¹¹⁸ K. Venkataraman, "The Chemistry of Synthetic Dyes," Vol. 2, Chapt. XXV, p. 761. Academic Press, New York, 1952.

¹¹⁹ H. Beecken, E. M. Gottschalk, U. v. Gizeycki, H. Krämer, D. Maassen, H. G. Matthies, H. Musso, C. Rathjen, and U. I. Záhorszky, *Angew. Chem.* **73**, 665 (1961).

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The Hilbert-Johnson Reaction of 2,4-Dialkoxypyrimidines with Halogenoses

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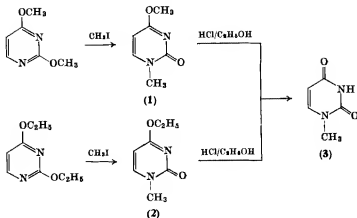
I. Introduction

After a successful preparation^{1,2} of 1-methyl-4-methoxy-2(1*H*)-pyrimidinone (**1**) and 1-methyl-4-ethoxy-2(1*H*)-pyrimidinone (**2**) by treatment of 2,4-dimethoxy- and 2,4-diethoxypyrimidine, respectively, with methyl iodide at room temperature, Hilbert and Johnson extended^{1,3} this reaction to poly-*O*-acylglycosyl halides, e.g., 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide (**4**). Upon heating the reactants at 50° for 48 hours (without solvent), an *N*-1-glycosyl derivative (**5**) was obtained in 23-32% yield. Similar to the formation of *N*-1-methyluracil (**3**) from **1** or **2**, the intermediate (**5**) afforded the "uracil-D-glucoside" (**6**) by the action of hydrogen chloride in ethanol.

¹ T. B. Johnson and G. E. Hilbert, *Science* **69**, 579 (1929).

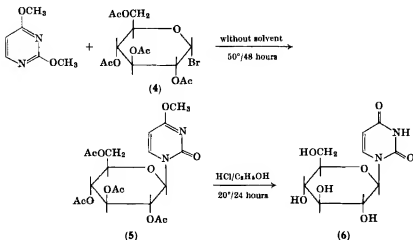
² G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 2001 (1930).

³ G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 4489 (1930).



Treatment of the intermediate (7), prepared⁴ from 2,4-diethoxy-pyrimidine and α -acetobromoglucose, with ethanolic ammonia afforded⁴ "cytosine-D-glucoside" (8).

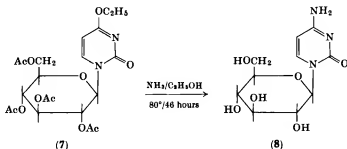
Many years later, Davoll *et al.*⁵ reinvestigated the above experiments^{3, 4} and ascribed the structure of 1-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)-4-methoxy-(or ethoxy)-2(1*H*)-pyrimidinone to the



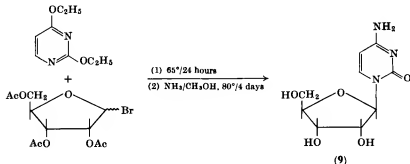
⁴ G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.* **58**, 60 (1936).

⁵ J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.* p. 833 (1946).

intermediates **5** or **7**, respectively. The final products are thus 1- β -D-glucopyranosyluracil (**6**) and 1- β -D-glucopyranosylcytosine (**8**). An unequivocal proof of the anomeric nature of these compounds was connected with constitutional studies of the naturally occurring pyrimidine nucleosides.⁶



Further reactions have been performed with 2,4-diethoxypyrimidine as the basic component and 2,3,4-tri-*O*-acetyl-L-arabinopyranosyl bromide,⁷ 2,3,4-tri-*O*-acetyl- α -D-xylopyranosyl bromide,⁷ 2,3,4,6-tetra-*O*-acetyl- α -D-galactopyranosyl bromide,⁷ and 2,3,4-tri-*O*-acetyl-D-ribosepyranosyl bromide⁸ as halogenoses; the products

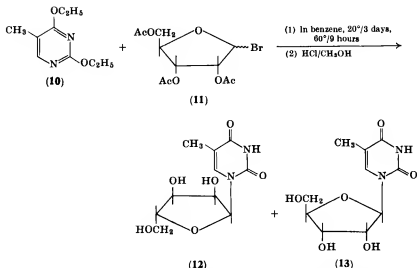


were converted by simultaneous deacetylation and dealkylation with methanolic hydrogen chloride into the corresponding 1-glycopyranosyluracils, but the configuration at the glycosidic center remained undetermined.

⁶ V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.* p. 2952 (1951).

⁷ G. E. Hilbert, *J. Am. Chem. Soc.* **59**, 330 (1937).

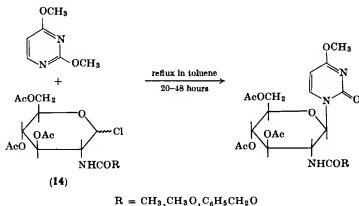
⁸ G. E. Hilbert and C. E. Rist, *J. Biol. Chem.* **117**, 371 (1937).



The first naturally occurring pyrimidine nucleoside prepared⁹ by the Hilbert-Johnson reaction was cytidine (9).

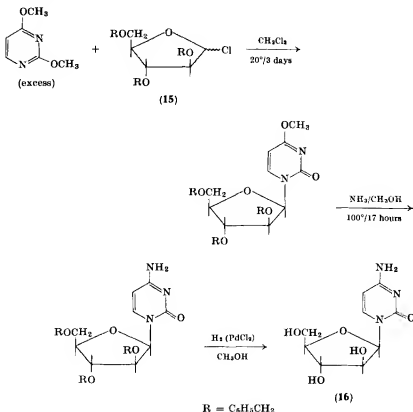
II. Scope and Limitations

The synthesis of cytidine⁹ by the Hilbert-Johnson procedure (which may be formulated as a reaction of 2,4-dialkoxypyrimidines with halogenoses) initiated further investigations in the field of the pyrimidine nucleoside synthesis. Thus, for example, the treatment of



⁹ G. A. Howard, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.* p. 1052 (1947).

2,4-diethoxy-5-methylpyrimidine (10) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (11) (at 60°, without solvents) was reported¹⁰ in 1952 to yield, upon hydrolysis, "5-methyluridine." This product was



reinvestigated by Fox *et al.*¹¹ and identified as an α anomer. Moreover, it has been shown¹¹ that both anomers, i.e., 1- α -D-ribofuranosylthymine (12) and 1- β -D-ribofuranosylthymine (5-methyluridine) (13), are formed in yields of 8.5 and 8.0%, respectively, when the reaction is performed in benzene as solvent.

Similarly, with 2,3,4-tri-*O*-benzoyl- β -D-ribofuranosyl bromide, a mixture of 1- α -D- and 1- β -D-ribofuranosylthymines was obtained.¹²

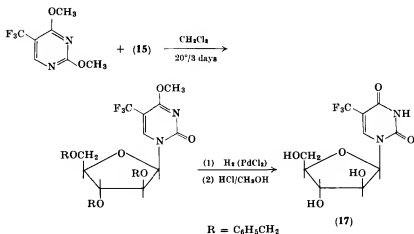
¹⁰ M. Roberts and D. W. Visser, *J. Am. Chem. Soc.* **74**, 668 (1952).

¹¹ J. Farkaš, L. Kaplan, and J. J. Fox, *J. Org. Chem.* **29**, 1469 (1964).

¹² T. Naito and T. Kawakami, *Chem. Pharm. Bull. (Tokyo)* **10**, 627 (1962).

The Hilbert-Johnson reaction of a protected 2-amino-2-deoxy-D-glucopyranosyl chloride (**14**) has been used in the synthesis of amino sugar nucleosides.¹³

It is of interest that both α -(*cis*) and β -(*trans*)acetobromoglucose yielded the same 1- β -D-glucopyranosyluracil.¹⁴ Recently, some exotic



halogenoses have been applied successfully in the Hilbert-Johnson reaction, namely 4-*O*-*p*-nitrobenzoyl-2,3,6-trideoxy-D-erythrohexopyranosyl chloride,¹⁵ 4,6-di-*O*-*p*-nitrobenzoyl-2,3-dideoxy-D-erythrohexopyranosyl chloride,¹⁶ and 3,4-di-*O*-*p*-nitrobenzoyl-2,6-dideoxy- β -D-ribohexopyranosyl chloride.¹⁷

2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl chloride (**15**), presumably of the α configuration, has been used¹⁸ in the synthesis of 1- β -D-arabinofuranosylecytosine (**16**) and 1- β -D-arabinofuranosyl-5-trifluoromethyluracil (**17**). In this case, the Hilbert-Johnson reaction has been performed at room temperature in methylene chloride as solvent. The unusual benzyl protecting groups were removed smoothly by hydro-

¹³ C. L. Stevens and K. Nagarajan, *J. Med. Pharm. Chem.* **5**, 1124 (1962).

¹⁴ J. J. Fox and I. Goodman, *J. Am. Chem. Soc.* **73**, 3256 (1951).

¹⁵ C. L. Stevens, N. A. Nielsen, P. Blumbergs, and K. G. Taylor, *J. Am. Chem. Soc.* **86**, 5695 (1964).

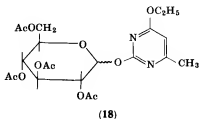
¹⁶ C. L. Stevens, N. A. Nielsen, and P. Blumbergs, *J. Am. Chem. Soc.* **86**, 1894 (1964).

¹⁷ W. W. Zorbach and G. J. Durr, Jr., *J. Org. Chem.* **27**, 1474 (1962).

¹⁸ T. Y. Shen, H. M. Lewis, and W. V. Ruyle, *J. Org. Chem.* **30**, 835 (1965).

genolysis. All the halogenoses hitherto used in the Hilbert-Johnson reaction are listed in Table I (see Section XII); Table II (see Section XII) shows the 2,4-dialkoxypyrimidine reaction components.

Of 2,4-dialkoxypyrimidines, only 2,4-di-*tert*-butoxypyrimidine¹⁹ and 5-nitro-2,4-dimethoxypyrimidine²⁰ failed to react in the normal Hilbert-Johnson fashion, and anomalous *O*-2-glycosyl derivatives have been obtained²¹ with a 2,4-dialkoxypyrimidine substituted in position 6, namely, with 2,4-diethoxy-6-methylpyrimidine; anomeric 2-tetra-*O*-acetyl-D-glucopyranosyloxy-4-ethoxy-6-methylpyrimidines (18) resulted. Unsuccessful attempts to synthesize an *N*-1-ribofuranosyl derivative of orotic acid (uracil-6-carboxylic acid) have been reported.²²



Application of 2,4-bis(trimethylsilyloxy)pyrimidines²³⁻²⁵ instead of 2,4-dialkoxypyrimidines is mentioned in the section dealing with modified Hilbert-Johnson reactions (Section III).

Recently, a systematic study on the Hilbert-Johnson reaction has been undertaken by Šorm *et al.*²⁶ Thus the role of solvents, various substituents in position 5 of the pyrimidine component, and various protecting groups in the sugar component have been investigated with a special regard to the total yield of the reaction and to the ratio of the resulting α and β anomers (see Section IX, dealing with the stereochemistry of the Hilbert-Johnson reaction).

¹⁹ M. Prystaš and F. Šorm, *Collection Czech. Chem. Commun.* **31**, 1035 (1966).

²⁰ M. Prystaš and F. Šorm, *Collection Czech. Chem. Commun.* **30**, 1900 (1965).

²¹ P. Newmark and I. Goodman, *J. Am. Chem. Soc.* **79**, 6446 (1957).

²² A. M. Michelson, W. Drell, and H. K. Mitchell, *Proc. Natl. Acad. Sci. U.S.A.* **37**, 396 (1951).

²³ T. Nishimura and I. Iwai, *Chem. Pharm. Bull. (Tokyo)* **12**, 352 (1964).

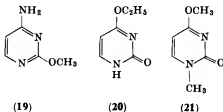
²⁴ T. Nishimura and I. Iwai, *Chem. Pharm. Bull. (Tokyo)* **12**, 357 (1964).

²⁵ T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull. (Tokyo)* **12**, 1471 (1964).

²⁶ M. Prystaš, J. Farkaš, and F. Šorm, *Collection Czech. Chem. Commun.* **28**, 3140 (1963).

III. Modifications

The Hilbert–Johnson reaction was originally performed without any solvent, simply by heating the reactants at temperatures ranging from 50 to 115°, eventually under reduced pressure^{12, 17, 27, 28} (to remove the alkyl halide arising in the reaction). An improved yield was reported when the reaction was performed in chloroform in the presence of a molecular equivalent of pyridine,²⁹ but no notice has been taken of this observation by subsequent authors. Refluxing



benzene as solvent has been recommended by Stevens and Nagarajan¹³ and then successfully used, e.g., by Fox *et al.*¹¹ Other solvents—toluene, acetonitrile, nitromethane, and sulfur dioxide, in the presence or absence of molecular sieves (as hydrogen chloride acceptors) or mercuric bromide—are mentioned in connection with the stereochemistry (see Section IX). Hilbert–Johnson reactions in methylene chloride at room temperature have been recently reported by Shen *et al.*¹⁸

Attempts to use basic reaction components other than 2,4-dialkoxy-pyrimidines met with varied success. Thus, the early attempt of Hilbert³⁰ to react α -acetobromoglucose with 4-amino-2-methoxy-pyrimidine (19) failed. On the other hand, when 4-ethoxy-2(1H)-pyrimidinone (20) or 1-methyl-4-methoxy-2(1H)-pyrimidinone (21) was condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride, moderate yields were obtained of 3- β -D-ribofuranosyluracil (22) and its 1-methyl derivative (23), respectively.³¹

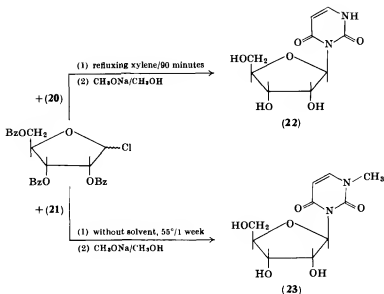
²⁷ D. W. Visser, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.* **70**, 1926 (1948).

²⁸ H. T. Miles, *J. Am. Chem. Soc.* **79**, 2565 (1957).

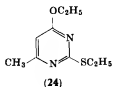
²⁹ J. L. Rabinowitz and S. Gurin, *J. Am. Chem. Soc.* **75**, 5758 (1953).

³⁰ G. E. Hilbert, *J. Am. Chem. Soc.* **56**, 190 (1934).

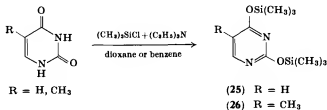
³¹ J. P. Scanell and F. W. Allen, *J. Org. Chem.* **25**, 2143 (1960).



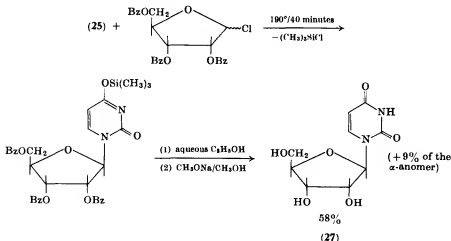
The reaction²¹ of α -acetobromoglucose with 2-ethylthio-4-ethoxy-6-methylpyrimidine (24) resulted in the formation of both anomeric *O*-4-glycosyl derivatives (the 2-ethylthio function remained intact).



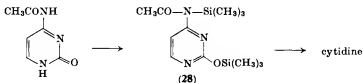
The so-called bis(trimethylsilyl) derivatives of uracil, thymine, and acetylcytosine (25, 26, 28) were found to be readily accessible²³ and to undergo the Hilbert-Johnson reaction at about 195°. Thus, for



example, the reaction²⁵ of 2,4-bis(trimethylsilyloxy)pyrimidine (25) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride followed by removal of the benzoyl groups afforded 58% of uridine (27) and 9% of the corresponding α anomer. Analogously, 2-trimethylsilyloxy-4-(*N*-acetyl-*N*-trimethylsilyl)aminopyrimidine (28) gave cytidine.



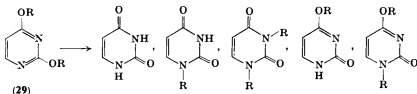
It may be expected that this novel modification of the Hilbert-Johnson reaction using the 2,4-bis(trimethylsilyloxy)pyrimidines will play an important role (cf. also the glycosidation of tetrakis-trimethylsilyluric acid or 2-trimethylsilyloxypyridine in Section VII dealing with related reactions).



IV. Side Reactions

The by-products which arose in the course of the Hilbert-Johnson reaction and were isolated either directly from the reaction mixture or after the usual work-up with alcoholic hydrogen chloride, hydrogen chloride in chloroform, or alcoholic ammonia might be divided into

four groups: (1) by-products formed from the basic component, (2) by-products formed from the sugar component, (3) by-products arising from the intermediate protected 1-glycosyl-4-alkoxy-2(1*H*)-pyrimidinones, and (4) the already mentioned "*O*-nucleosides." The occurrence of most by-products is due to hydrogen halide arising by a partial decomposition of the halogenose (2-deoxyhalogenoses, especially, are relatively unstable.) For this reason it is advisable to



use suitable molecular sieves as hydrogen chloride acceptors when the Hilbert-Johnson reaction is carried out in solvents. When the reaction is performed without solvents it is recommended that the resulting alkyl halides be removed by reduction of the pressure because of danger of an undesired reaction with the starting 2,4-dialkoxypyrimidines, especially at elevated temperatures.

(1) Under conditions of the Hilbert-Johnson reaction, the 2,4-dialkoxypyrimidines (29) can furnish the following by-products: uracil,¹³ 1-alkyluracil,^{3, 7} 1,3-dialkyluracil,¹⁹ 4-alkoxy-2(1*H*)-pyrimidinone,⁷ and 1-alkyl-4-alkoxy-2(1*H*)-pyrimidinone.^{7, 20} Thus, for example, 5-chloro-, 5-bromo-, and 5-iodouracil were isolated^{32, 33} as by-products in the Hilbert-Johnson reaction (in acetonitrile at 20°) of the corresponding 5-halo-2,4-dimethoxypyrimidines and 3,5-di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride. The formation of 1,3-dimethyluracil and 1,3,5-trimethyluracil as by-products has been observed quite recently¹⁹ when the reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride with 2,4-dimethoxypyrimidine and 5-methyl-2,4-dimethoxypyrimidine, respectively, was performed in toluene at 70°.

(2) The use of 2-deoxy-D-ribofuranosyl chlorides protected at positions 3 and 5 with *p*-toluyl, *p*-nitrobenzoyl, or *p*-chlorobenzoyl groups is usually accompanied by the formation of the corresponding

³² M. Prystaš and F. Šorm, *Collection Czech. Chem. Commun.* **29**, 121 (1964).

³³ M. Prystaš and F. Šorm, *Collection Czech. Chem. Commun.* **29**, 131 (1964).

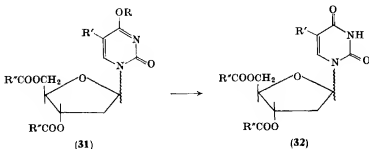
furfuryl esters of *p*-toluic,³⁴ *p*-nitrobenzoic,³⁵ or *p*-chlorobenzoic³⁵ acids or the free acids alone. The structure of 3-*p*-toluyloxy-2,5-(*p*-toluyloxyendomethylene)tetrahydrofuran (**30**) has been ascribed²⁰ to a by-product of the Hilbert-Johnson reaction (at -2°) of 5-fluoro-2,4-dimethoxypyrimidine with 3,5-di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride in acetonitrile as solvent.



(30)



(3) In some cases, the primary *O*-4-alkyl intermediates of the type **31** are transformed by traces of hydrogen chloride into the dealkylated intermediates of the type **32** protected only in the sugar moiety. Thus,

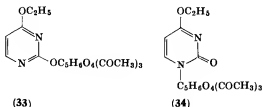


for example, the Hilbert-Johnson reaction of 5-chloro- and 5-bromo-2,4-dimethoxypyrimidine, respectively, with 3,5-di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride afforded³³ the anomeric 1-(3,5-di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl)-5-halouracils (**32**, $R' = \text{Cl}$ or Br , $R'' = p\text{-CH}_3\text{C}_6\text{H}_4\text{CO}$) in addition to the expected anomeric 1-(3,5-di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl)-4-methoxy-5-halo-2(1*H*)-pyrimidinones (**31**, $R = \text{CH}_3$, $R' = \text{Cl}$ or Br , $R'' = p\text{-CH}_3\text{C}_6\text{H}_4\text{CO}$).

³⁴ M. Prystaš, J. Farkaš, and F. Šorm, *Collection Czech. Chem. Commun.* **30**, 3123 (1965).

³⁵ M. Prystaš and F. Šorm, *Collection Czech. Chem. Commun.* **30**, 2960 (1965).

(4) Isolation of an "*O*-nucleoside" as the by-product was reported for the first time by Hilbert and Rist⁸: 2-(2,3,4-tri-*O*-acetyl-*D*-ribo-pyranosyloxy)-4-ethoxypyrimidine (**33**) was obtained in addition to



the expected 1-(2,3,4-tri-*O*-acetyl-*D*-ribo-pyranosyl)-4-ethoxy-2(1*H*)-pyrimidinone (**34**) on treatment (65°/18 hours) of acetobromo-*D*-ribo-pyranose with 2,4-diethoxypyrimidine. 6-Substituted 2,4-dialkoxypyrimidines, in particular, have been reported²¹ to tend to form *O*-2-glycosyl derivatives (cf. Section II). The structural variation of 2,4-dialkoxypyrimidines in the Hilbert-Johnson reaction seems thus to be limited²¹ to substitution at position 5.

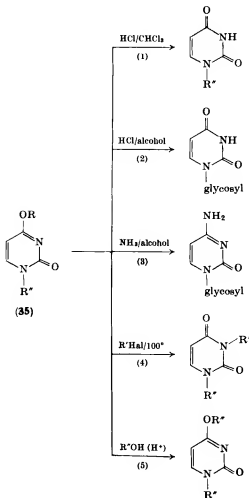
V. Miscellaneous Uses of the Hilbert-Johnson Products

The primary products of the Hilbert-Johnson reaction, 1-peracylglycosyl-4-alkoxy-2(1*H*)-pyrimidinones (**35**), can be worked up (see Scheme I) in various ways, e.g., (1) by dealkylation^{13, 19, 20, 26, 32-35} with hydrogen chloride in chloroform to give 1-peracylglycosyluracils; (2) by a simultaneous^{3, 8, 10, 11} dealkylation and deacylation with hydrogen chloride in an alcohol to give the free 1-glycosyluracils; (3) by a simultaneous^{4, 5, 9} replacement of the 4-alkoxy group by an amino group and deacylation with ammonia in alcohol to give the free 1-glycosylcytosines; (4) by a rearrangement^{28, 36} with alkyl halides at elevated temperatures to give 3-alkyl-1-peracylglycosyluracils; and (5) by a H⁺-catalyzed exchange¹⁹ of the 4-alkoxy group by another 4-alkoxy group.

VI. Configuration of the Hilbert-Johnson Products

The most reliable determination of the configuration of the Hilbert-Johnson products at the anomeric center consists in correlation with

³⁶ M. Prystaš and F. Šorm, unpublished results.



SCHEME I. Work-up of the Hilbert-Johnson intermediates. R, R' = alkyl; R'' = peracylglycosyl.

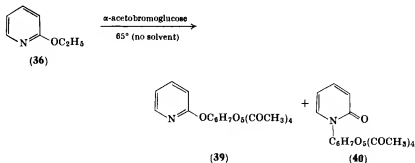
naturally occurring nucleosides of known constitution, their derivatives, or periodate oxidation products.^{5, 37} On the other hand, the

³⁷ J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.* **78**, 2117 (1956).

Baker *trans* rule or the Hudson isorotation rules have to be taken with care in view of some anomalies.^{11, 38, 39} Nuclear magnetic resonance spectra³⁸ and optical rotatory dispersion curves^{38, 40, 41} have been recently applied to determine the configuration of pyrimidine nucleosides at the anomeric center.

VII. Related Reactions

Instead of 2,4-dialkoxypyrimidines, some other alkoxy heterocyclics capable of lactam-lactim tautomerism were used, e.g., 2-ethoxypyridine^{42, 43} (36), 4-ethoxypyridine⁴⁴ (37), and 3,6-dibenzyloxy-pyridazine⁴⁵ (38). Treatment of α -acetobromoglucose with 36 gave



a mixture of acetylated 2-glucosyloxypyridine (39) and 1-glucosyl-2-pyridone (40), whereas 4-ethoxypyridine (37) afforded the acetylated 1-glucosyl-4-pyridone (41) as the sole product.

The synthesis of maleic acid hydrazide riboside (42) has been accomplished⁴⁵ by the Hilbert-Johnson reaction of 38 with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in toluene at 100° in the presence

³⁸ R. U. Lemieux and M. Hoffer, *Can. J. Chem.* **39**, 110 (1961).

³⁹ J. J. Fox, N. C. Yung, I. Wempen, and M. Hoffer, *J. Am. Chem. Soc.* **83**, 4066 (1961).

⁴⁰ T. L. V. Ulbricht, J. P. Jennings, P. M. Scopes, and W. Klyne, *Tetrahedron Letters* p. 695 (1964).

⁴¹ I. Frie, J. Smejkal, and J. Farkas, *Tetrahedron Letters* p. 75 (1966).

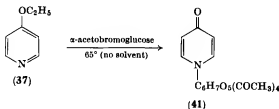
⁴² G. Wagner and H. Pischel, *Arch. Pharm.* **295**, 373 (1962).

⁴³ G. Wagner and H. Pischel, *Arch. Pharm.* **296**, 699 (1963).

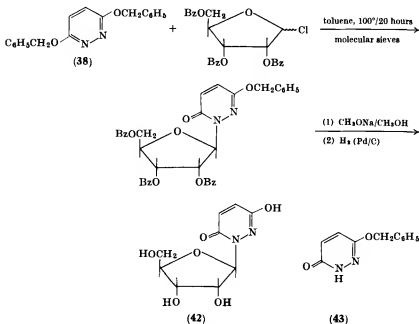
⁴⁴ G. Wagner and H. Pischel, *Arch. Pharm.* **295**, 897 (1962).

⁴⁵ J. Pliml and F. Šorm, *Collection Czech. Chem. Commun.* **30**, 3744 (1965).

of molecular sieves, with subsequent debenzoylation and debenzylation. In the absence of molecular sieves, a considerable amount of 6-benzyloxy-3(2*H*)-pyridazinone (**43**) was isolated as by-product.

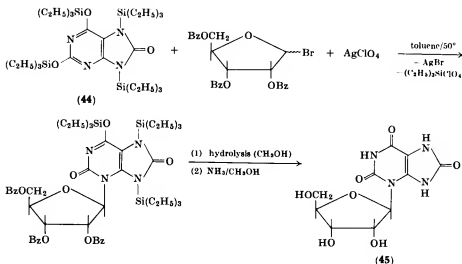


A high yield of 3- β -D-ribofuranosyluric acid (**45**) has been obtained^{46, 47} on treatment of tetrakis(triethylsilyl)uric acid (**44**) with benzobromoribofuranose at 50° in the presence of silver perchlorate in toluene as solvent, subsequent hydrolysis with methanol, and removal of the protecting benzoyl groups with methanolic ammonia.



⁴⁶ L. Birkofer, A. Ritter, and H. P. K hlthau, *Chem. Ber.* **97**, 934 (1964).

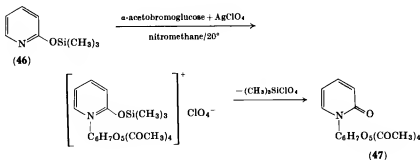
⁴⁷ L. Birkofer and A. Ritter, *Angew. Chem.* **77**, 414 (1965).



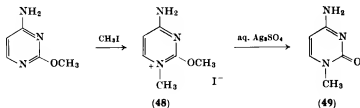
Similarly, treatment of 2-trimethylsilyloxypyridine (46) with α -acetobromoglucose and silver perchlorate in nitromethane at 20° yielded 1-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-2-pyridone (47) as the sole product.^{46, 47} On the other hand, 2-ethoxypyridine (*vide supra*) gave a mixture of *O*- and *N*-glycosyl derivatives.^{42, 43}

VIII. Mechanism

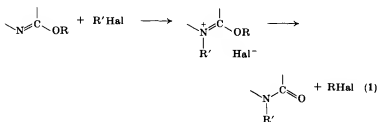
The reaction of a 2,4-dialkoxypyrimidine with a halogenose (or an alkyl halide) has been assumed by Hilbert³⁰ to proceed via a quaternary salt as intermediate. Thus, the stable 1-methyl-2-methoxy-4-



aminopyrimidinium iodide (48) has been obtained³⁰ from 2-methoxy-4-aminopyrimidine and methyl iodide (but not with a halogenose). Treatment of the quaternary salt (48) with aqueous silver sulfate yielded 1-methylcytosine (49).



Later on, the following general scheme was proposed by Ulbricht⁴⁸ for the Hilbert-Johnson reaction involving quaternization of nitrogen followed by attack by halide ion [Eq. (1)].

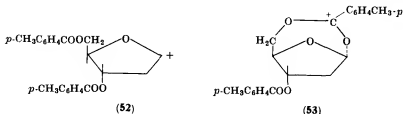


The course of the Hilbert-Johnson reaction in different solvents has been studied recently by Šorm *et al.*^{19, 35} In polar solvents, an ionization of the halogenose occurs in accordance with Ulbricht.⁴⁸ The cation formed, which is somewhat stabilized (by solvation and neighboring group participation of the 2-acyloxy group), then reacts with the poorly nucleophilic 2,4-dialkoxy-4-aminopyrimidine. In this case, the reaction is highly stereospecific. In poorly polar solvents, the ionic pair of the halogenose may be assumed to take part in the reaction to a certain degree. In this case, the steric course of the reaction is dependent on the original configuration of the halogenose and 1-peracylglycosyl-4-alkoxy-2(1*H*)-pyrimidinones result possessing an opposite configuration at the anomeric center. Formation of the *O*-2-glycosyl derivatives^{8, 21} in the Hilbert-Johnson reaction might be explained as follows. In view of the low electron density on *N*-1 atom,

⁴⁸ T. L. V. Ulbricht, *J. Chem. Soc.* p. 3345 (1961).

⁴⁹ M. Prvstaš and F. Šorm, *Collection Czech. Chem. Commun.* **31**, 1053 (1966).

The steric course of the above deoxyribosylations might be explained by the formation of the cation (52) which is readily attacked by a nucleophile from the α -position. An attack from the opposite side is hindered by the bulky *p*-toluyl group at position 5 of the sugar moiety. Moreover, the cation (52) might be stabilized by a transannular participation of the *C*-5-*p*-toluyl group with the formation of the

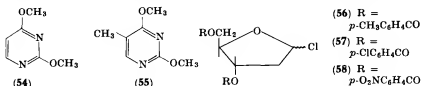


cyclic ion (53) which should afford stereospecifically the α anomer. As shown,³⁵ however, by the Hilbert-Johnson reaction of 2,4-dimethoxypyrimidine (54) or 5-methyl-2,4-dimethoxypyrimidine (55) with 2-deoxy-D-ribofuranosyl chlorides (56, 57, and 58) protected by blocking groups of a different participation ability, namely, by *p*-toluyl, *p*-chlorobenzoyl, and *p*-nitrobenzoyl groups, the steric effect of the *C*-5-acyl group predominates over the transannular participation effect.

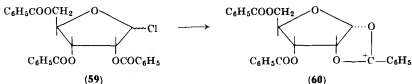
The influence³⁶ of solvents on the ratio of the α anomer to the β anomer is shown in Table III (see Section XII). It has been found that the α anomer considerably predominated when the Hilbert-Johnson reaction of the bases 54 or 55 with the halogenoses 56, 57, and 58 was performed in polar solvents, e.g., in acetonitrile or nitromethane. On the other hand, in poorly polar solvents, e.g., in benzene or toluene, the value of the ratio α anomer/ β anomer is lower, but the α anomer still predominates.

The reactivity (in acetonitrile as solvent) of various 2,4-dialkoxy-pyrimidines¹⁹ towards 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (59) was found to decrease in the order 2,4-dibenzyloxy-, 2,4-bis(*p*-methoxybenzyloxy)-, 2,4-dimethoxy-, 2,4-diethoxy-, 2,4-bis(2,4-dimethoxybenzyloxy), 2,4-diisopropoxypyrimidine. In all these cases, the β anomer represented the sole reaction product. In view of this stereospecificity, the reaction of the halogenose (59) with the above 2,4-dialkoxy-pyrimidines represents a procedure of choice for preparation of uridine or cytidine and their derivatives. When the Hilbert-

Johnson reaction of the halogenose (59) with the bases (54 or 55) was performed in benzene, a small amount of the corresponding α anomer accompanied the main reaction product, the β anomer. Formation of



the α anomer in a poorly polar solvent might be explained by involvement of an ion pair arising from the halogenose (59). On the other hand, in a polar solvent, the halogenose (59), predominantly of the β configuration, forms an orthoester cation (60) from which only a β anomer can result.



The Hilbert-Johnson reaction of 5-halo-2,4-dimethoxypyrimidines with the halogenose (59) in acetonitrile or benzene as solvents afforded good yields of the corresponding 1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-4-methoxy-5-halo-2(1*H*)-pyrimidinones free of α anomers.⁵⁰

The reaction⁵¹ of 5-methyl-2,4-diethoxypyrimidine with perbenzoylated D-arabino-, D-xylo-, and D-lyxofuranosyl bromides in polar solvents (acetonitrile, nitromethane) proceeds stereospecifically with the formation of *C*-1'-*C*-2'-*trans* derivatives whereas in poorly polar solvents (e.g., toluene) the corresponding *C*-1'-*C*-2'-*cis* derivatives are also formed.

Peracylglycopyranosyl halides (α -acetobromoglucopyranose,^{1, 3-5} 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-D-glucopyranosyl chloride¹³) react with 2,4-dialkoxypyrimidines with the formation of *C*-1'-*C*-2'-*trans* derivatives whereas the corresponding *cis* derivatives were encountered rarely (e.g., in the reaction with 2,3,4-tri-*O*-acetyl- β -D-ribopyranosyl bromide¹²).

⁵⁰ M. Prysaš and F. Šorm, *Collection Czech. Chem. Commun.* **29**, 2956 (1964).

⁵¹ J. Šmejkal, J. Farkaš, and F. Šorm, *Collection Czech. Chem. Commun.* **32**, in press (1967).

X. Experimental Conditions

Absence or presence of *solvents* seems to play an important role in the Hilbert–Johnson reaction. Generally, better results are obtained in the presence of solvents,¹³ but, unfortunately, no systematic comparisons have been performed so far. In some cases, it was possible to change the ratio of α anomers to β anomers by variation of polarity of the solvents.^{34, 35} The reaction *time* depends strongly on the reactivity and stability of the halogenose used. Thus, for example, the Hilbert–Johnson reaction of 2,4-dimethoxypyrimidine (in acetonitrile at room temperature) with 3,5-di-*O-p*-toluyl-2-deoxy-D-ribofuranosyl chloride requires 1–2 hours for completion,¹⁹ whereas storage of the reaction mixture for several days is necessary with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride.^{34, 35} An even longer period of time is necessary in the case of peracylglycopyranosyl halides. The Hilbert–Johnson reaction of relatively stable and less reactive halogenoses can be performed at elevated temperatures, e.g., in boiling solvents, whereas with reactive and relatively unstable halogenoses, room temperature is recommended. Some reactions²⁰ have been carried out at 0° (e.g., with 5-fluoro-2,4-dimethoxypyrimidine as the basic component). By the use of *molecular sieves*^{19, 20, 35, 45, 49, 50} as hydrogen chloride acceptors, the formation of various by-products (cf. Section IV) is largely suppressed.

Recently, the use of *mercuric bromide* (in acetonitrile or benzene) in the Hilbert–Johnson reaction has been investigated.^{20, 35, 49} Thus, with 3,5-di-*O-p*-toluyl-2-deoxy-D-ribofuranosyl chloride, the reaction rate was higher in the presence of one or more molar equivalents of mercuric bromide, but the total yield of the anomeric mixture was considerably decreased because of the rapid decomposition of the deoxyhalogenose; the amount of the β anomer in the anomeric mixture increased in this case. With stable halogenoses,^{49, 50} the use of mercuric bromide leads to shorter reaction times (the total yield is not lowered to such an extent as with deoxyhalogenoses).

The Isolation Technique; Chromatography. Two alternatives are possible: either to isolate the primary Hilbert–Johnson intermediates, i.e., 1-peracylglycosyl-4-alkoxy-2(1*H*)-pyrimidinones, or to treat them with alcoholic hydrogen chloride or alcoholic ammonia and separate the corresponding *N*-1-glycosyl derivatives of uracil or cytosine. The latter alternative has been used by the earlier authors more frequently because of the higher crystallization ability of

nucleosides. Later, chromatography on cellulose, or paper chromatography,⁵¹ was used as the final purification procedure of the nucleosides obtained. In most cases, however, it is more advantageous to separate the peracyl intermediates, especially when both anomers are formed. Excellent results in this respect have been obtained^{19, 20, 26, 32-35, 45, 49, 50} with column or thin layer chromatography over neutral alumina. Thus, the mixtures are applied to a column of alumina packed in benzene and the elution is performed with benzene-ethyl acetate solvent mixtures containing increasing amounts of ethyl acetate. By this procedure, mixtures²⁰ containing only a few milligrams of α and β anomers or very complicated mixtures containing many by-products have been separated almost quantitatively.³²⁻³⁵ The importance of a suitable separation procedure might be illustrated by isolation (chromatography on Magnesol) of 1-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)-4-ethoxy-5-methyl-2(1*H*)-pyrimidinone²⁸ which has been overlooked by earlier investigators⁵² though it has been obviously present.

XI. Comparison with Other Methods of Nucleoside Synthesis

In addition to the Hilbert-Johnson reaction, the so-called mercuri process,³⁷ and, less frequently, the cyclization procedure of Shaw *et al.*,^{53, 54} have been used for the synthesis of nucleosides and their derivatives. 1-Peracylglycosyl-4-alkoxy-2(1*H*)-pyrimidinones, the intermediates of the Hilbert-Johnson reaction, can be, in principle, prepared^{55, 56} also by the mercuri process, namely by reaction of 4-ethoxy-2(1*H*)-pyrimidinone chloromercuri salt with the corresponding halogenoses, but this method is of less importance because of the contamination of *N*-1-glycosyl derivatives with the *O*-2 isomers, namely, with 2-peracylglycosyloxy-4-alkoxypyrimidines. The advantageous features of the mercuri process in comparison with the Hilbert-Johnson reaction might be formulated as follows.

The starting mercury salts of the pyrimidine component can be

⁵² W. Schmidt-Nickles and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 4511 (1930).

⁵³ R. K. Ralph and G. Shaw, *J. Chem. Soc.* p. 1877 (1956).

⁵⁴ G. Shaw, R. N. Warrenner, M. H. Maguire, and R. K. Ralph, *J. Chem. Soc.* p. 2294 (1958).

⁵⁵ J. J. Fox, N. Yung, I. Wempen, and I. L. Doerr, *J. Am. Chem. Soc.* **79**, 5060 (1957).

⁵⁶ T. Ukita, H. Hayatsu, and Y. Tomita, *Chem. Pharm. Bull. (Tokyo)* **11**, 1068 (1963).

prepared easily and in almost quantitative yields whereas the preparation of 2,4-dialkoxypyrimidines represents at least a two-step process. In some cases, however, the mercury salts are not uniform or fail to react with halogenoses (cf. the fruitless attempts⁵⁷ to prepare uridine by the mercuri process and the successful preparation of uridine by the Hilbert-Johnson reaction⁴⁹). Uridine substituted at position 5 with electronegative groups or 6-substituted uridines are accessible only with difficulty by the Hilbert-Johnson reaction^{20, 21} but can be prepared by the mercuri process^{58, 59} (e.g., orotidine has been obtained in 14.5% yield by condensing the monomercuri derivative of butyl orotate with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride and removing the protecting groups). Recently,⁶⁰ 1-(2-deoxy-D-glucopyranosyl)-5-fluorocytosine has been prepared by reaction of 5-fluoro-2,4-diethoxypyrimidine with 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl- α -D-arabinohexopyranosyl bromide followed by treatment with methanolic ammonia.

The products of the mercuri process in most cases possess a *C*-1'-*C*-2'-*trans* system in accordance to the Baker *trans* rule⁶¹⁻⁶⁴ and are sterically more uniform than the Hilbert-Johnson products. On the other hand, certain anomers inaccessible by the mercuri process may be obtained under certain conditions (solvent) by the Hilbert-Johnson reaction as a mixture with the other anomer; chromatographic methods have been worked out to separate these mixtures almost quantitatively into the individual anomers (cf. Section X). The Hilbert-Johnson reaction intermediates may be converted into nucleosides of both types, of the uridine type as well as of the cytidine type (cf. Section V), whereas conversion of the mercuri process of the uridine type into the cytidine type is somewhat tedious. On the whole, the Hilbert-Johnson reaction represents a suitable complementary method to the mercuri process.

⁵⁷ J. J. Fox and I. Wempfen, *Advan. Carbohydrate Chem.* **14**, 283 (1959).

⁵⁸ M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.* **81**, 4112 (1959).

⁵⁹ W. V. Curran and R. B. Angier, *Tetrahedron Letters* **8**, 533 (1963).

⁶⁰ G. J. Durr, *J. Med. Pharm. Chem.* **8**, 140 (1965).

⁶¹ B. R. Baker, *Ciba Found. Symp. Chem. Biol. Purines*, p. 120 (1957).

⁶² B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.* **19**, 1786 (1954).

⁶³ B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.* **77**, 2396 (1955).

⁶⁴ J. J. Fox, J. F. Codington, N. C. Yung, L. Kaplan, and J. O. Lampen, *J. Am. Chem. Soc.* **80**, 5155 (1958).

XII. Tabular Survey of Reactants (Tables I-III)

TABLE I

HALOGENOSES IN THE HILBERT-JOHNSON REACTION

Formula	Compound	References
C ₁₁ H ₁₅ BrO ₇	2,3,4-Tri- <i>O</i> -acetyl- β -D-arabinopyranosyl bromide	14, 27
	2,3,4-Tri- <i>O</i> -acetyl- β -L-arabinopyranosyl bromide	7, 14, 27
	2,3,4-Tri- <i>O</i> -acetyl- β -D-ribosepyranosyl bromide	8, 12, 27
	2,3,4-Tri- <i>O</i> -acetyl- α -D-xylopyranosyl bromide	7, 14
	2,3,5-Tri- <i>O</i> -acetyl-D-ribofuranosyl bromide	9-11
C ₁₁ H ₁₅ ClO ₇	2,3,4-Tri- <i>O</i> -acetyl- β -D-arabinopyranosyl chloride	14
	2,3,4-Tri- <i>O</i> -acetyl- β -L-arabinopyranosyl chloride	14
	2,3,4-Tri- <i>O</i> -acetyl- α -D-xylopyranosyl chloride	14
C ₁₂ H ₁₇ ClO ₇	3,4,6-Tri- <i>O</i> -acetyl-2-deoxy-D-glucopyranosyl chloride	66
C ₁₃ H ₁₄ ClNO ₅	4- <i>O</i> - <i>p</i> -Nitrobenzoyl-2,3,6-trideoxy-D-erythrohexopyranosyl chloride	15
C ₁₄ H ₁₉ BrO ₉	2,3,4,6-Tetra- <i>O</i> -acetyl- α -D-galactopyranosyl bromide	7, 14, 27
	2,3,4,6-Tetra- <i>O</i> -acetyl- α -D-glucopyranosyl bromide	1, 3-5, 14, 21, 24, 27-30, 46, 52
	2,3,4,6-Tetra- <i>O</i> -acetyl- α -D-mannopyranosyl bromide	7
C ₁₄ H ₁₉ ClO ₉	2,3,4,6-Tetra- <i>O</i> -acetyl- α -D-galactopyranosyl chloride	14
	2,3,4,6-Tetra- <i>O</i> -acetyl- α -D-glucopyranosyl chloride	14, 52
	2,3,4,6-Tetra- <i>O</i> -acetyl- β -D-glucopyranosyl chloride	14
C ₁₄ H ₂₀ ClNO ₈	3,4,6-Tri- <i>O</i> -acetyl-2-deoxy-2-acetamido-D-glucopyranosyl chloride	13
C ₁₄ H ₂₀ ClNO ₉	3,4,6-Tri- <i>O</i> -acetyl-2-deoxy-2-carbomethoxyamino-D-glucopyranosyl chloride	13
C ₁₉ H ₁₅ ClN ₂ O ₉	3,5-Di- <i>O</i> - <i>p</i> -nitrobenzoyl-2-deoxy-D-ribofuranosyl chloride	35

TABLE I—continued

Formula	Compound	References
$C_{19}H_{15}Cl_3O_5$	3,5-Di- <i>O-p</i> -chlorobenzoyl-2-deoxy-D-ribofuranosyl chloride	35
$C_{20}H_{17}ClN_2O_9$	4,6-Di- <i>O-p</i> -nitrobenzoyl-2,3-dideoxy-D-erythrohexopyranosyl chloride	16
	3,4-Di- <i>O-p</i> -nitrobenzoyl-2,6-dideoxy- β -D-ribohexopyranosyl chloride	17
$C_{20}H_{24}ClNO_9$	3,4,6-Tri- <i>O</i> -acetyl-2-deoxy-2-carbo-benzyloxyamino- α -D-glucopyranosyl chloride	13
$C_{21}H_{21}ClO_5$	3,5-Di- <i>O-p</i> -toluyl-2-deoxy-D-ribofuranosyl chloride	20, 26, 32-35, 45, 49
$C_{26}H_{21}BrO_7$	2,3,5-Tri- <i>O</i> -benzoyl-D-arabinofuranosyl bromide	51
	2,3,5-Tri- <i>O</i> -benzoyl-D-lyxofuranosyl bromide	51
	2,3,5-Tri- <i>O</i> -benzoyl-D-ribofuranosyl bromide	46, 51
	2,3,5-Tri- <i>O</i> -benzoyl-D-xylofuranosyl bromide	51
$C_{26}H_{21}ClO_7$	2,3,5-Tri- <i>O</i> -benzoyl-D-ribofuranosyl chloride	19, 25, 31, 45, 49, 50
$C_{26}H_{27}ClO_4$	2,3,5-Tri- <i>O</i> -benzyl-D-arabinofuranosyl chloride	18
$C_{27}H_{20}ClN_3O_{13}$	3,4,6-Tri- <i>O-p</i> -nitrobenzoyl-2-deoxy- α -D-arabinohehexopyranosyl bromide	17, 60

TABLE II

BASIC COMPONENTS IN THE HILBERT-JOHNSON REACTION

Formula	Compound	Reference
$C_6H_7BrN_2O_2$	5-Bromo-2,4-dimethoxypyrimidine	33, 50
$C_6H_7ClN_2O_2$	5-Chloro-2,4-dimethoxypyrimidine	33, 50
$C_6H_7FN_2O_2$	5-Fluoro-2,4-dimethoxypyrimidine	20, 50
$C_6H_7IN_2O_2$	5-Iodo-2,4-dimethoxypyrimidine	32, 50

TABLE II—continued

Formula	Compound	Reference
$C_6H_8N_2O_2$	2,4-Dimethoxypyrimidine	1-3, 5, 13, 18, 19, 26, 28, 34, 35
	4-Ethoxy-2(1 <i>H</i>)-pyrimidinone	31
	1-Methyl-4-methoxy-2(1 <i>H</i>)-pyrimidinone	31
$C_7H_7N_3O_2$	5-Cyano-2,4-dimethoxypyrimidine	65
$C_7H_7F_3N_2O_2$	5-Trifluoromethyl-2,4-dimethoxy- pyrimidine	18
$C_7H_{10}N_2O_2$	5-Methyl-2,4-dimethoxypyrimidine	19, 26, 34, 35, 52
$C_8H_{11}FN_2O_2$	5-Fluoro-2,4-diethoxypyrimidine	60
$C_8H_{11}N_3O_3$	5-Acetamido-2,4-dimethoxypyrimidine	65
$C_8H_{12}N_2O_2$	2,4-Diethoxypyrimidine	4, 7-9, 14-16, 19, 51, 66
$C_9H_{14}N_2O_2$	5-Methyl-2,4-diethoxypyrimidine	10, 11, 12, 14, 17, 27, 28
$C_{10}H_{16}N_2O_2$	2,4-Diisopropoxypyrimidine	19
$C_{10}H_{20}N_2O_2Si_2$	2,4-bis(Trimethylsilyloxy)pyrimidine	24, 25
$C_{11}H_{22}N_2O_2Si_2$	5-Methyl-2,4-bis(trimethylsilyloxy)- pyrimidine	24, 25
$C_{12}H_{23}N_3O_2Si_2$	2-Trimethylsilyloxy-4-(acetyltrimethyl- silyl)aminopyrimidine	24, 25
$C_{14}H_{16}N_2O_3$	5-Benzoyloxymethyl-2,4-dimethoxy- pyrimidine	49
$C_{18}H_{16}N_2O_2$	2,4-Dibenzoyloxypyrimidine	19
$C_{20}H_{20}N_2O_4$	2,4-bis(<i>p</i> -Methoxybenzyloxy)pyrimidine	19
$C_{22}H_{24}N_2O_6$	2,4-bis(2,4-Dimethoxybenzyloxy)- pyrimidine	19
<i>Anomaly</i>		
$C_9H_{14}N_2OS$	2-Ethylthio-4-ethoxy-6-methyl- pyrimidine	21
$C_9H_{14}N_2O_2$	6-Methyl-2,4-diethoxypyrimidine	21, 29
<i>Failure</i>		
$C_8H_7N_3O_2$	2-Methoxy-4-aminopyrimidine	30
$C_8H_7N_3O_4$	5-Nitro-2,4-dimethoxypyrimidine	20
$C_{12}H_{20}N_2O_4$	2,4-Di- <i>tert</i> -butoxypyrimidine	19

⁶⁵ M. Prystaš and F. Šorm, *Collection Czech. Chem. Commun.* **31**, 3990 (1966).⁶⁶ J. J. Fox, L. F. Cavalieri, and N. Chang, *J. Am. Chem. Soc.* **75**, 4315 (1953).

TABLE III

THE ANOMERIC RATIO OF PRODUCTS OF THE HILBERT-JOHNSON REACTION OF DIMETHOXYPYRIMIDINES (54 AND 55) WITH HALOGENOSES (56, 57, AND 58) IN ACETONITRILE (PROCEDURE A) AND IN BENZENE (PROCEDURE B)

Reactants		Procedure	Ratio of the α anomer to the β anomer	Over-all yield (%)
Halogenose	Base			
56	54	A	7.7	61
		B	3.4	36
56	55	A	5.7	74
		B	2.5	52
57	54	A	4.5	50
		B	2.4	31
57	55	A	3.6	46
		B	1.9	39
58	54	A	5.7	44
		B	3.4	35
58	55	A	3.8	39
		B	1.9	36

Claisen Rearrangements in Nitrogen Heterocyclic Systems

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I. Introduction

For over five decades, since its discovery in the year 1912, the Claisen rearrangement of aryl allyl ethers into the corresponding *C*-allyl phenols has held considerable interest for organic chemists—from the mechanistic as well as the synthetic aspects. Angular alkylations in natural products like kaurene, otherwise difficult to achieve, have been effected successfully by means of this facile rearrangement.¹ On the mechanistic front, however, despite the concerted onslaught of many able investigators, the rearrangement has earned for itself the title, “No-mechanism rearrangement”² in view of the absence of clearly discernible and distinctive electronic preferences in its transition state.

During these five decades, the rearrangement has also evoked much interest in its extensions into the nitrogen and oxygen heterocyclic systems. The present review is an attempt to present some of the chemistry relating to nitrogen heterocyclic compounds wherein the

¹ R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Letters*, p. 1 (1960).

² S. J. Rhoads, “Molecular Rearrangements” (P. de Mayo, Ed.), Pt. I. Wiley (Interscience), New York, 1963.

allyl ether is located on the hetero ring system (as in the pyridine moiety of a quinoline derivative). No rearrangements from molecules containing other hetero atoms are discussed. The material is divided, for the sake of convenience, into sections dealing with the different ring systems like pyridine, quinoline, pyrimidine, etc.

One common feature in these molecules is the fact that the presence of an electron-rich center like the nitrogen atom tends to pull the allylic chain into itself. Consequently, migrations to other positions in these molecules are less often encountered. However, where migrations to carbon atoms do occur, much interesting chemistry relating to mechanistic pathways has resulted. Aspects of these developments are presented in the following pages.

II. Synthesis of the Allyl Ethers

The synthesis of the allyl ethers in nitrogen heterocyclic systems presents an element of complication in that the allylation could occur on the oxygen atom or the basic nitrogen atom. This is a feature of alkylation of ambident anions.³ However, this applies only when the allylation is effected by reacting the oxo or hydroxy derivative of the compound with an allyl halide in the presence of a base.^{3a} The alternative method is to react the appropriate halo derivative with sodium allyloxide in allyl alcohol. The latter approach provides not only better yields of the allyl ethers but also certainty of the constitution of the ethers obtained. A diagnostic tool in deciding between the 1-allyl derivative and the *O*-allyl compound that has commonly been employed is the infrared absorption of the amide carbonyl in the case of the former which is clearly absent in the latter.

In the case of the pyridine derivatives, the differences in the ultra-

³ E. Klingsberg (Ed.), "The Chemistry of Heterocyclic Compounds," Pt. 3, p. 633. Wiley (Interscience), New York, 1962.

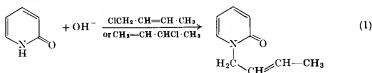
^{3a} In a paper⁴ that has often been overlooked as a contribution to the study of Claisen rearrangement of pyridyl and quinolyl allyl ethers (largely because it emphasized in its title the synthesis of antimalarial compounds) the allyl ethers were obtained by reacting hydroxyquinolines and hydroxypyridines with allyl bromide in acetone in the presence of potassium carbonate as base. None of the products from such a reaction was examined to verify if they were *N*-allyl or *O*-allyl derivatives. These were then subjected to rearrangement in refluxing alpha methylnaphthalene and the products of rearrangement were assumed to be the corresponding *C*-allylhydroxypyridines and quinolines.

⁴ W. Saltzer, H. Timmler, and H. Andersag, *Ber.* **81**, 12 (1948).

violet absorption characteristics of the 1-allyl pyridones and the 2-allyloxy pyridine derivatives are prominent enough to be used as a diagnostic tool.⁵ Thus the pyridones absorb at 225–230 $m\mu$ and at 295–300 $m\mu$ while the allyloxy pyridines show a single maximum in the region 255–260 $m\mu$.

More recently, NMR spectra have also been employed to determine the positions of the allyl functions.⁶

An additional element of complication in preparing the allyl ethers utilizing the salts of hydroxypyridines lies in the intervention of S_N2' displacements. Thus the sodium salt of 2-pyridone on treatment with crotyl chloride or with 3-chloro-1-butene afforded the same compound, viz., 1-crotyl-2-pyridone⁵ [Eq. (1)].



Allyloxy derivatives from pyridine-1-oxides posed still a further element of uncertainty. This arose from the facile isomerization of 2-alkoxy pyridine-1-oxides into the corresponding 1-alkoxy-2-pyridones even under the conditions of synthesis. Thus, treatment of 2-chloropyridine-1-oxide with sodium allyl alcoholate afforded the 2-allyloxy pyridine-1-oxide whereas treatment of the same starting compound with sodium benzyloxide gave 1-benzyloxy-2-pyridone. A closer investigation revealed that 2-benzyloxy pyridine-1-oxide rearranged readily under the experimental conditions of synthesis.⁶

One is thus faced with three different possibilities in preparing allyl ethers from the hydroxy derivatives of nitrogen heterocyclic systems, viz. (1) the possibility of alkylation on the nitrogen; (2) the alkylation occurring on the oxygen; and (3) the possibility of rearrangements even under the conditions of synthesis. However, the three different types of structures may well be distinguished from one another on the basis of their extensive physical properties like their ultraviolet, infrared, and NMR spectra as well as basicity measurements. In an elegant study involving tautomerism of hydroxypyridine derivatives the broad basis of such distinguishing features has been well-discussed.⁷

⁵ F. J. Dinan and H. Tieckelmann, *J. Org. Chem.* **29**, 892 (1964).

⁶ F. J. Dinan and H. Tieckelmann, *J. Org. Chem.* **29**, 1650 (1964).

⁷ J. N. Gardner and A. R. Katritzky, *J. Chem. Soc. p.* 4375 (1957).

III. General Conditions of Rearrangements

The Claisen rearrangement in nitrogen heterocyclic systems has been carried out in many different solvents. The ease of allylic migration appears to vary considerably among the different systems. The solvent media commonly employed are diethylaniline, 1-methylnaphthalene, and *N,N*-diethyl-*m*-toluidine (b.p., 231°). In other instances, where the allyl ethers are liquids, the rearrangement has also been effected without any solvent. Under these conditions, the results are not always the same as those observed with a solvent.

In general, systems incorporating more than one nitrogen atom seem to rearrange faster and at lower temperatures. Thus, 2-allyloxybenzimidazole rearranges at 180° quantitatively.⁸ 7-Allyloxy-*s*-triazolo-(1,5-*a*)pyrimidine rearranges at 150° within 30 minutes.⁹ Purine derivatives rearrange even at 100°.¹⁰ Increasing the nucleophilicity of the migration terminus also appears to enhance the ease of migration. Thus 2-allyloxypyridine-1-oxide rearranges to 1-allyloxy-2-pyridone at 100° in 3 hours.⁶

The rearrangements could often be followed by the change in the ultraviolet absorption spectra (as in the case of the allyloxypyridine-1-oxides) or through quantitative analysis by paper chromatography of the product mixture (as in the case of the pyrimidine derivatives) or by gas liquid chromatography and infrared spectral analysis (as in the case of the quinoline derivatives).

Although, on the basis of the enhanced nucleophilicity of the ring nitrogen atom, one would normally expect a prosaic pattern of migration of allyl groups to the nitrogen in most of these systems, allylic migration has often been observed to proceed to a ring carbon atom, even in preference to the adjacent nitrogen. It is features like these that have contributed to the enhanced interest in the study of the Claisen rearrangements in nitrogen heterocyclic systems.

IV. Rearrangements and Mechanistic Features

A. PYRIDINE SERIES

The earliest report on the Claisen rearrangement of allyl ethers in the pyridine series was by Saltzer *et al.*⁴ Reaction of 2,6-dimethyl-4-pyridone with allyl bromide and crotyl bromide was assumed to give

⁸ S. Takahashi and H. Kano, *Chem. Pharm. Bull. (Tokyo)* **12**, 282 (1964).

⁹ Y. Makisumi, *Chem. Pharm. Bull. (Tokyo)* **11**, 851 (1963).

¹⁰ E. Bergmann and H. Heimbold, *J. Chem. Soc. p.* 1365 (1935).

the respective *O*-allyl compounds and these were rearranged in α -methyl-naphthalene. The products on the basis of their elemental analyses were assumed to be 3-allyl-2,6-dimethyl-4-pyridone and 3-crotyl-2,6-dimethyl-4-pyridone.^{10a} No spectral characterization of either the starting materials or the products was reported, nor was the possibility of the allylic inversion investigated. The presence of the methyl group at the 2 and 6 positions may have hindered migration of the allyl function to the nitrogen atom.

In a more recent investigation¹¹ Moffett prepared 4-allyloxypyridine by reacting 4-bromopyridine with sodium allyloxide. Attempts to rearrange this compound led largely to polymeric products. No characterizable rearrangement product could be isolated.

3-Allyloxypyridine was difficult to prepare. Treatment of the sodium salt of 3-hydroxypyridine with allyl bromide resulted in attack mostly on the nitrogen. No rearrangement could therefore be attempted on this derivative.

The synthesis of 2-allyloxypyridine and 2-crotyloxypyridine had been described earlier by Russian workers.¹² Reacting 2-chloropyridine with the corresponding sodium alkoxide afforded the ethers. The best conditions for the rearrangement of these ethers were found to be heating in refluxing diethylaniline.⁵ From 2-allyloxypyridine were obtained 3-allyl-2-pyridone, 1-allyl-2-pyridone, 2-pyridone, and much uncharacterizable resin. This clearly indicated that the migration occurs not only to the more nucleophilic nitrogen but also to the β position of the ring.

In a more extensive study devoted to the mechanistic aspects of these rearrangements, Dinan and Tieckelmann⁵ investigated the behaviour of three different allyl ethers by heating them in dimethylaniline solution in a sealed tube at 255°. Their results are summarized in Eq. (2). The starting materials and products are shown in Table I.

The products thus revealed that a normal Claisen migration had occurred with inversion of the allylic side chain.

Some differences were noticed, however, when the same ethers were rearranged neat without solvent. In the rearrangement of 2-allyloxypyridine and 2-(1-methylallyloxy)pyridine, the results were no

^{10a} In this Chapter, structures which the original authors drew as hydroxy-compounds have been changed to the more likely keto-compounds.—Ed.

¹¹ R. B. Moffett, *J. Org. Chem.* **28**, 2885 (1963).

¹² B. I. Mikhentev, E. I. Federov, A. I. Kucherova, and V. P. Potopova, *Zh. Obshch. Khim.* **29**, 1874 (1959).

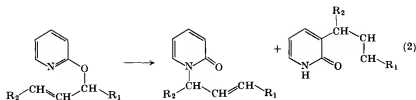
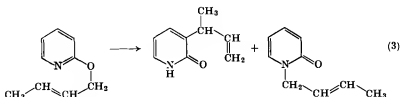


TABLE I
REARRANGEMENT OF ALLYLOXYPYRIDINES

Starting ether	Time (hours)	Product	Yield (%)
(1) 2-Allyloxypyridine	7	1-Allyl-2-pyridone	40-55
		3-Allyl-2-pyridone	35-40
(2) 2-Crotyloxypyridine	4	1-(1-Methylallyl)-2-pyridone	40-55
		3-(1-Methylallyl)-2-pyridone	35-40
(3) 2-(1-Methylallyloxy)pyridine	12	1-Crotyl-2-pyridone	40-55
		3-Crotyl-2-pyridone	35-40

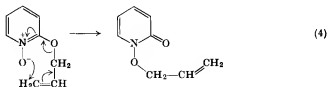
different. But in the case of 2-crotyloxypyridine one of the products showed no allylic inversion [Eq. (3)].



From a study of the rearrangement as a function of time, Dinan and Tieckelmann found that the normal product 1-methylallyl-2-pyridone was initially formed in large amounts. But the ratio of the "abnormal product," namely the 1-crotyl-2-pyridone, to the normal product increased as the reaction proceeded longer. When rearrangement was complete, there was some 40-60% of the abnormal product in the mixture of isomers. When a pure sample of 1-(1-methylallyl)-2-pyridone was subjected to the same experimental conditions, no isomerization was observable nor did the compound reverse to the

starting ether. It was also verified that the starting ether itself did not isomerize prior to the rearrangement. Thus no 2-(1-methylallyloxy)pyridine was obtainable from 2-crotyloxy pyridine under the experimental conditions. Besides, the migration to the ring carbon atom, as seen above, occurs normally with allylic inversion.

Extending these studies to pyridine 1-oxides, Dinan and Tieckelmann investigated the behavior of 2-allyloxy pyridine-1-oxide.⁶ The ether was prepared by nucleophilic displacement of chlorine from 2-chloropyridine-1-oxide by sodium allyloxide. Rearrangement of this compound was complete within 3½ hours at 100°. Essentially quantitative yields of 1-allyloxy-2-pyridone were obtained [Eq. (4)].



The enhanced yields of a single product and the lower temperature required for migration in this instance points to the ease of attack by the anionic 1-oxide oxygen on the allylic side chain. These rearrangements were unaffected by the presence of benzoquinone, indicating absence of radical intermediates.

In a contemporaneous investigation, Thyagarajan *et al.*¹³ prepared the two ethers 4-allyloxy pyridine-1-oxide and 4-cinnamyloxy pyridine-1-oxide by nucleophilic displacement of either 4-nitro- or 4-chloropyridine-1-oxide at room temperature using the appropriate alkoxides. However, attempts to rearrange the ethers led to much tar formation and little tractable material.

B. QUINOLINE SERIES

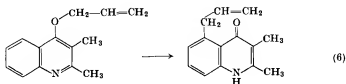
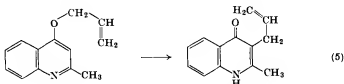
Rearrangements of allyloxyquinolines were carried out as early as 1924.¹⁴ 2-Allyloxyquinoline was prepared by reacting 2-chloroquinoline with sodium allyloxide in allyl alcohol. The ether was rearranged by heating it to 325–329°. 1-Allyl-2-quinolone was isolated as the product. Even attempted distillation of the starting ether at atmospheric pressure resulted in the formation of the quinolone. The 1-allyl-2-

¹³ B. S. Thyagarajan, K. K. Balasubramanian, and R. Bhima Rao, unpublished results, 1964.

¹⁴ A. E. Tschitschibabin and N. P. Jeletzky, *Ber.* **57B**, 1158 (1924).

quinolone was characterized by an independent synthesis using the potassium salt of carbostyryl and allyl bromide.

Some 8 years later, Mander-Jones and Trikojus¹⁵ investigated the behavior of 4-allyloxyquinoline derivatives. Rearrangement of 4-allyloxy-2-methyl-quinoline gave a product to which was assigned the structure 2-methyl-3-allyl-4-quinolone [Eq. (5)]. Similar rearrangement of 4-allyloxy-2,3-dimethylquinoline was, however, assumed to give a product containing the allyl group on the benzenoid ring [Eq. (6)].



In their work on antimalarial compounds, Saltzer *et al.*⁴ also effected similar rearrangements. In every instance, the products were assumed to be the corresponding 3-allyl-4-quinolones (see Table II).

TABLE II
REARRANGEMENTS OF ALLYLOXYQUINOLINES

Starting quinoline	Product
(1) 4-Allyloxy-2-methylquinoline	2-Methyl-3-allyl-4-quinolone
(2) 7-Methoxy-4-allyloxy-2-methylquinoline	7-Methoxy-2-methyl-3-allyl-4-quinolone
(3) 7-Methoxy-4-crotyloxy-2-methylquinoline	7-Methoxy-2-methyl-3-(1-methylallyl)-4-quinolone
(4) 5-Methoxy-4-allyloxy-2-methylquinoline	5-Methoxy-2-methyl-3-allyl-4-quinolone

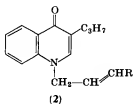
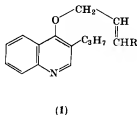
¹⁵ B. Mander-Jones and V. M. Trikojus, *J. Am. Chem. Soc.* **54**, 2570 (1932).

No substantial evidence was provided for any of these structures.

The most thorough and systematic investigation into the behavior of allyloxyquinolines has been carried out by Makisumi in the last 2 years.¹⁸⁻¹⁹ These investigations have shed much light into the mechanistic features of the Claisen rearrangements as applicable to nitrogen heterocyclic systems.

All the rearrangements in the quinoline series were effected neat without solvents at 200°. Yields were almost quantitative in almost all the instances although more than one product often resulted from a single starting material. The common feature of allylic inversion was clearly established in these migrations. The intermediacy of the cyclohexadienone-type structure was also demonstrated.

Allyl and crotyl ethers were prepared from 3-propyl-4-quinolones by two different approaches. Displacement of 4-chloro-3-propylquinoline by the sodium salt of the two alcohols gave the ethers (1) as clean products, whereas reacting 3-propyl-4-hydroxyquinoline with allyl bromide in the presence of sodium ethoxide afforded not only the allyl ether but also the 1-allylquinolone (2). The products were well-characterized by their ultraviolet spectra and infrared bands. Rearrangement of the ethers at 200° without solvent gave quantitative yields of the corresponding 1-allyl-3-propyl-4-quinolones (2).



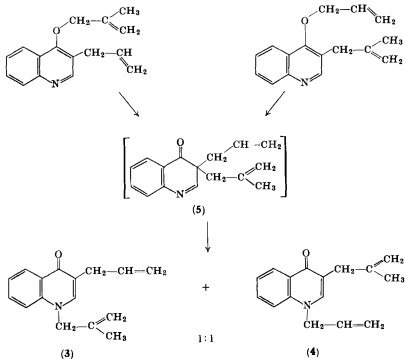
Further support for this observation was secured from a study of the rearrangement of the two ethers 3-allyl-4-methallyloxyquinoline and 4-allyloxy-3-methallylquinoline. The quinolone product obtained in quantitative yields in both cases was found by infrared spectral analysis to be a 1:1 mixture of the two possible structures (3 and 4).

¹⁶ Y. Makisumi, *Tetrahedron Letters*, p. 699 (1964).

¹⁷ Y. Makisumi, *Tetrahedron Letters*, p. 1635 (1964).

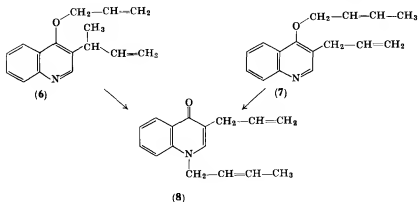
¹⁸ Y. Makisumi, *J. Org. Chem.* **30**, 1986 (1965).

¹⁹ Y. Makisumi, *J. Org. Chem.* **30**, 1989 (1965).



Thus it was established that 3-substituted 4-allyl ethers of quinoline rearrange to the nitrogen atom rather than to the benzene ring.

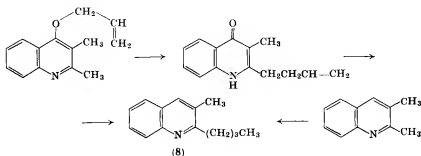
In order to verify the possibility of the intervention of a cyclohexadienone-type intermediate (5) in the rearrangement to the



nitrogen atom, compounds **6** and **7** were synthesized and rearranged. The same single product, namely 3-allyl-1-crotyl-4-quinolone (**8**), was obtained in quantitative yields from both the ethers. This clearly indicates that the migration to the nitrogen atom involves a double inversion of the allylic side chain and that the methylallyl group migrates in preference to the allyl group. This latter observation is attributed to the inductive effect of an α -methyl group in accelerating the migration as well as the relief of steric strain in the cyclohexadienone intermediate by the migration of the more crowded group.

The fact that irrespective of the nature of the starting compound, in the two ethers described above, the same ratio of the two products was observed again emphasizes the intermediacy of a dienone structure.

In a sequential study, Makisumi¹⁹ investigated the behavior of 4-quinolyl ethers carrying alkyl groups in the 2 and 3 positions of the molecule. Mander-Jones and Trikojus^{15, 20} had reported allylic migration to the benzene ring under these conditions. The compound obtained by rearrangement of 4-allyloxy-2,3-dimethylquinoline had been assigned the 5-allyl-2,3-dimethyl-4-quinolone structure [Eq. (6)]. Makisumi's reinvestigation has shown that this assignment was wrong and that, even in these instances where the 2 and 3 positions carry alkyl groups, allylic migration occurs to the pyridinoid part of the quinoline ring system.

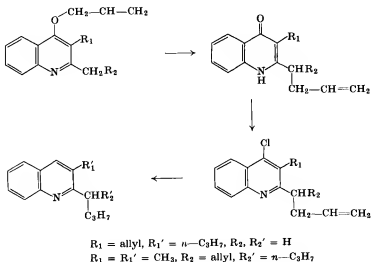


4-Allyloxy-2,3-dimethylquinoline on heating without a solvent at 200° for only 30 minutes afforded in yields as high as 92% a product with a quinolone structure. Confirmation of this formulation came from the following series of transformations: (1) treatment with phosphorus oxychloride which gave the 4-chloro compound; and

²⁰ B. Mander-Jones and V. M. Trikojus, *Proc. Roy. Soc. N. S. Wales* **66**, 300 (1932); *Chem. Abstr.* **27**, 1350 (1933).

(2) hydrogenation to remove the chlorine and saturate the side chain. This resulted in the formation of 2-butyl-3-methylquinoline (9). This compound was synthesized by an alternative approach starting from 2,3-dimethylquinoline.

With a view to establishing the generality of this observation, Maki-sumi studied the rearrangement of the following other 4-allyloxyquinoline derivatives, also under similar conditions. In every instance, the reaction went to completion within 30 minutes and gave an excellent yield of the product incorporating the allyl side chain on the methyl group at the 2 position (Scheme 1).



SCHEME 1

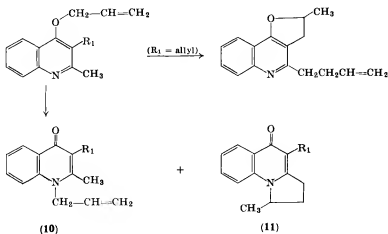
The structures of these products were established by hydrogenation to the corresponding saturated compounds, and the latter were synthesized by alternative methods.

Although the major product of rearrangement in the above instances carried the allylic function on the 2-methyl group, other products shown below were also isolated in small yields.

The 1-allyl compound (10) and the tricyclic product (11) were shown to arise by independent pathways rather than by sequential migration from the *C*-allyl derivatives described above. Thus under

the experimental conditions for the over-all rearrangement, all the products were stable to further transformations.

The Claisen rearrangement of allyl ethers in the quinoline series is thus seen to be unusually fast, affording high yields of products. In no case has migration of the allyl side-chain to the benzenoid ring been observed. Migrations to the nitrogen atom and to the alkyl side-chain proceed by concurrent rather than consecutive paths.



C. PYRIMIDINE SERIES

Studies in the rearrangement of allyl ethers in the pyrimidine series have been carried mainly by Tieckelmann and co-workers.^{21, 21a} Here again the possibility exists for the allyl group to migrate either to the adjacent nitrogen atom or to a ring carbon atom. Both types of products are encountered. However, contrary to the ease of migration observed in the quinoline series, where the yields were almost quantitative and reaction times short, all rearrangements in the pyrimidine series required temperatures above 200° and much longer duration of heating (4 to 8 hours). The best yields were no greater than 28%. The pyrimidine system thus appears to resemble the pyridyl allyl ethers.

The allyloxypyrimidines, prepared from the corresponding halo-

²¹ H. J. Minnemeyer, J. A. Egger, J. F. Holland, and H. Tieckelmann, *J. Org. Chem.* **26**, 4425 (1961).

^{21a} F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.* **28**, 1015 (1963).

pyrimidines and sodium allyloxide, are shown in Table III with the derived products of rearrangement.^{21a}

TABLE III
REARRANGEMENT OF PYRIMIDINES

Starting pyrimidine	Product	Yield (%)
(1) 2-Methylthio-4-allyloxy-pyrimidine	2-Methylthio-5-allyl-4-pyrimidone	22
(2) 2-Benzylthio-4-allyloxy-pyrimidine	2-Benzylthio-5-allyl-4-pyrimidone	28
(3) 2-Amino-4-allyloxy-pyrimidine	2-amino-5-allyloxy-4-pyrimidone	2-14 (yields were erratic)
(4) 2-Methyl-4-allyloxy-pyrimidine	Did not rearrange	—
(5) 2-Trifluoromethyl-4-allyloxy-pyrimidine	Did not rearrange	—
(6) 2-Methylthio-4-crotyloxy-pyrimidine	2-Methylthio-5-(1-methylallyl)-4-pyrimidone	—

When the residue from one of these above rearrangements (that of 2-benzylthio-4-allyloxypyrimidine) was investigated more closely it revealed the following components: 2-benzylthio-5-allyl-4-pyrimidone, 24%; 2-benzylthio-3-allyl-4-pyrimidone, 30%; 2-benzylthio-4-hydroxy-5-allylpyrimidine, 10%; 2-benzylthio-4-pyrimidone, 2%; 2-benzylthio-4-allyloxypyrimidine, 20%; unidentified material, 9%; and unisolable material, 5%.

The rearrangement of these ethers showed the same general mechanistic features as observed in the benzene series. Thus, 2-methylthio-4-crotyloxypyrimidine led to 2-methylthio-5-(1-methylallyl)-4-pyrimidone with allylic inversion. When a mixture of 2-methylthio-4-allyloxypyrimidine and 2-benzylthio-4-crotyloxypyrimidine were rearranged together, there was no evidence of cross-over products, indicating that the over-all process was intramolecular. The products once formed were stable to the experimental conditions suggesting the irreversibility of the initial migration. Therefore, the 3-allyl and the 5-allyl compounds must arise by competing migrations of the 4-allyl group to either of the *ortho* positions.

In a more recent reinvestigation of the pyrimidine series, H. J. Minnemeyer *et. al.*^{22a} obtained the percentages of rearrangements shown in Table IV.

TABLE IV
REARRANGEMENT OF PYRIMIDINES

Starting pyrimidine	Product	Yield (%)
(1) 2-Methylthio-4-allyloxy-pyrimidine	2-Methylthio-5-allyl-4-pyrimidone	32
	2-Methylthio-3-allyl-4-pyrimidone	19
(2) 2-Benzylthio-4-allyloxy-pyrimidine	2-Benzylthio-5-allyl-4-pyrimidone	34
	2-Benzylthio-3-allyl-4-pyrimidone	14
(3) 2-Methyl-4-allyloxypyrimidine	2-Methyl-3-allyl-4-pyrimidone	16
	2-Methyl-5-allyl-4-pyrimidone	25
(4) 2-Phenyl-4-allyloxypyrimidine	2-Phenyl-5-allyl-4-pyrimidone	36
	2-Phenyl-3-allyl-4-pyrimidone	14
(5) 2-Trifluoromethyl-4-allyloxy pyrimidine	"Gives no observable ortho-rearrangement products"	—

D. BENZIMIDAZOLE SERIES

Allyl ethers situated on the imidazole moiety in this system show interesting behavior. 2-Allyloxybenzimidazole affords a quantitative yield of 1-allyl-2-(3*H*)-benzimidazolinone on heating at 180° [Eq. 7]^{22b}. On the other hand, 1-allyloxybenzimidazole (**12**) does not rearrange on heating even at its decomposition point. This observation is in line with the findings in the pyridine series where 2-allyloxypyridine-1-oxide rearranges irreversibly to the 1-allyloxy-2-pyridone.

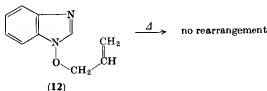
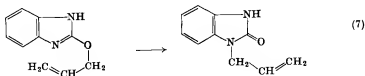
Under the same experimental conditions, 2-ethoxybenzimidazole does not rearrange. When heated to higher temperatures, 200–230°, a

^{22a} H. J. Minnemeyer, P. B. Clarke, and H. Tieckelmann, *J. Org. Chem.*, **31**, 406 (1966).

^{22b} S. Takahashi and H. Kano, *Chem. Pharm. Bull. (Tokyo)* **12**, 282 (1964).

mixture of 2-(3*H*)-benzimidazolinone and 1-ethyl-2-ethoxybenzimidazole were obtained. Thus the allyl ether migrates faster and in higher yields.^{22b}

Thyagarajan *et al.*^{22c} have recently investigated the Claisen rearrangement of 2-(phenoxyethyl)-benzimidazole and 2-(*p*-chlorophenoxyethyl)benzimidazole under a variety of conditions. Heating neat at 290–300° resulted in tar formation and isolation of a small quantity of *p*-chlorophenol from the latter instance. Refluxing in diethylaniline or ethylene glycol for 8 to 15 hours only gave back starting material. Refluxing in diphenyl ether under nitrogen afforded much tar and none of the rearranged products. These attempts were made to see if replacement of a C=C by a C=N would afford normal Claisen rearrangement products, however, this did not happen.



E. TRIAZOLOPYRIMIDINE SERIES

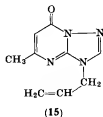
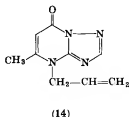
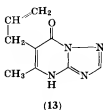
Studies of allyl ether migrations in this system have stemmed solely from the efforts of Makisumi.^{23, 24} By reacting 5-methyl-7-chloro-*s*-triazolo-(1,5-*a*)pyrimidine with sodium allyloxide in allyl alcohol at room temperature, the corresponding 7-allyloxy derivative was obtained. When this was rearranged at 150°, during 30 minutes, seven different products were obtained. These were separated into chloroform-soluble and chloroform-insoluble material. Out of the latter, by fractional crystallization two products were isolated. One of these was

^{22c} B. S. Thyagarajan, K. K. Balasubramanian, and R. Bhima Rao, unpublished results 1965.

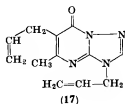
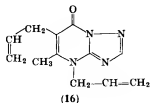
²³ Y. Makisumi, *Chem. Pharm. Bull. (Tokyo)* **11**, 851 (1963).

²⁴ Y. Makisumi, *Chem. Pharm. Bull. (Tokyo)* **11**, 859 (1963).

identified as 5-methyl-7-hydroxy-*s*-triazolo-(1,5-*a*)pyrimidine by comparison with an authentic specimen. In this instance, the allyl group had been completely lost, thus indicating the possibility that the allylic side-chain might find itself on other sites of the parent system by pathways other than intramolecular migration. The second component of the chloroform-insoluble part was isomeric with the starting material and showed ultraviolet absorption maxima at 247 and 279 $m\mu$. On this basis, it was assigned the 5-methyl-6-allyl-7-hydroxy-*s*-triazolo-(1,5*a*)pyrimidine structure (13). From the chloroform-soluble part of the rearrangement product mixture, four more crystalline compounds were isolated. Of these two were found to be isomeric with the starting compound. On the basis of their ultraviolet absorption maxima, these were assigned the structures 14 and 15. Thus migration of the allylic function had occurred not only on the *ortho* position but also to the ring nitrogen in the *para* position and to the nitrogen of the triazole ring.



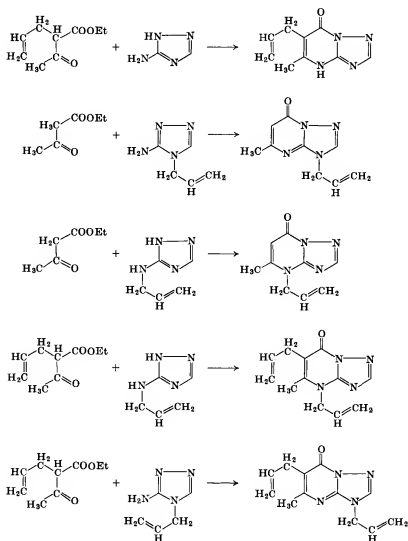
In addition to these three above, two other diallyl derivatives were identified. The structures of these products (16, 17) are shown below:



Apart from the spectral clues to their structures, these compounds were also synthesized by alternative independent methods. Condensation of ethyl 2-acetyl-4-pentenoate with 5-amino-*s*-triazole afforded

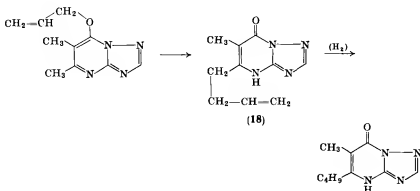
5-methyl-6-allyl-7-hydroxy-*s*-triazolo-(1,5-*a*)pyrimidine. Condensation of ethyl acetoacetate with *N*-allyl-5-amino-*s*-triazole afforded 3-allyl-5-methyl-7-oxo-*s*-triazolopyrimidine.

Scheme 2 summarizes the synthetic pathways leading to the



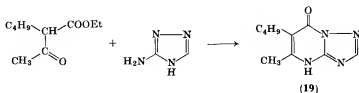
SCHEME 2

preparation of the Claisen rearrangement products. Thus the constitution of five of the seven products isolated was clearly established. In all these rearrangements, Makisumi considered the 6-allyl-5-methyl-7-oxo-*s*-triazolopyrimidine alone to arise from a straightforward *ortho*-Claisen rearrangement. The other products were suggested to form by intermolecular alkylation.

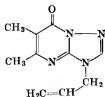


As an extension of this study, Makisumi investigated the behavior of 7-allyloxy-5,6-dimethyl-*s*-triazolo-(1,5-*a*)pyrimidine under similar conditions.²⁴ The objective was to determine the nature and site of migration of the allylic function when both the *o*-positions were blocked. This compound rearranged so readily that it could not be distilled *in vacuo*. Purified by chromatography, it rearranged within an hour at 180° giving a 66% yield of an isomeric product. On the basis of ultraviolet and nuclear magnetic resonance data, the compound was assigned structure 18.

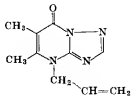
The alternative structure of attaching the allyl moiety at the 6 position was ruled out by synthesis of the reduction product (19) of that derivative along the following lines:



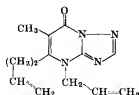
Of the five more products that were obtained from the same rearrangement, four were identified by the synthetic routes employed earlier, involving 1-allyl-5-amino-*s*-triazole and 5-allylamino-*s*-triazole. These structures (20-23) are illustrated below:



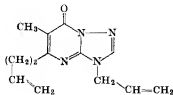
(20)



(21)

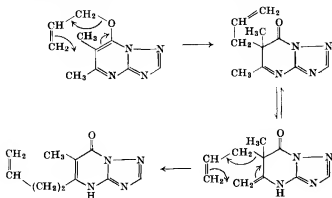


(22)



(23)

Thus once again migration occurs to the ring nitrogen atoms. However, the migration to the methyl group at 5 position is unusual and has been suggested to arise by the following mechanism (Scheme 3):



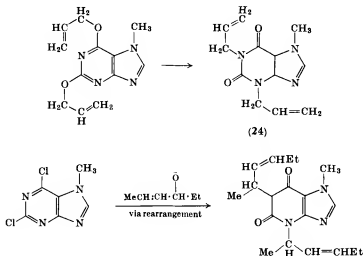
SCHEME 3

This is completely analogous to the similar observation made in the quinoline series where the allyl side-chain attaches itself to the 2-

methyl group in the quinoline ring. Together, these two constitute the first and unusual observations of such "out-of-ring" migrations of the allyl group in the Claisen rearrangement in nitrogen heterocyclic systems.

F. PURINE SERIES

Rearrangements of allyl ethers in the purines had been reported as early as 1935.²⁵ However, there is little scope for unusual migrations in this ring system owing to the nonavailability of positions other than the ring nitrogens for the attachment of the allyl moiety. Thus 2,6-diallyloxy-7-methylpurine, prepared from 2,6-dichloro-7-methylpurine and sodium allyloxide, on heating at 150° for 2 hours gave 1,3-diallyl-7-methylxanthine (**24**). Similarly the product from 2,6-dichloro-7-methylpurine and the sodium derivative of 2-hexen-4-ol rearranged so readily that it could not even be distilled *in vacuo*. The structures of the rearrangement products were established by hydrogenating them to the corresponding saturated derivatives.



²⁵ E. Bergmann and H. Heimhold, *J. Chem. Soc.* p. 1365 (1935).

ACKNOWLEDGMENTS

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Cyclic Peroxides *

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I. Introduction

This chapter deals with the formation and behavior of peroxides in which the O—O group forms part of a ring. The most important of these "heterocycles" are: *peroxides of carbonyl compounds*, which may also contain two or three peroxy groups in the same ring: *ozonides*, which are also peroxides of carbonyl compounds, i.e., peroxidic acetals; and *endoperoxides*, as cyclic dialkyl peroxides.

The ring may also contain other hetero atoms such as O, N, or S as well as the O—O group.

The development of peroxide chemistry has led to the publication

*Translated by Express Translation Service, London, England.

of many reviews and books,¹⁻⁷ in which the cyclic peroxides are dealt with in the discussion of peroxide chemistry as a whole. The only case in which they are treated separately is that of the book by Hawkins,¹ who devotes a chapter to the cyclic compounds. A number of reviews have been published on certain classes of cyclic peroxides; for example Bailey⁸ reported on ozonides, while Étienne⁹ discussed photooxides. Gollnick and Schenck¹⁰ recently wrote a paper on "Reactions of dienes with oxygen." The large number of recent developments, some of them very recent, in the field of cyclic peroxides has prompted us to compile this survey.

In the synthesis of cyclic peroxides, as in the synthesis of peroxides in general, the peroxy group must be introduced into the molecule as a single unit. This can be achieved with the aid of hydrogen peroxide, ozone, or oxygen. The formation of the peroxide bond in an organic molecule by linkage of two O fragments has so far been accomplished only in special cases,¹¹⁻¹⁴ and the formation of a peroxidic heterocycle by "spontaneous generation" of the O—O group has been described only in the case of organic fluorine compounds.¹²

Whereas the yield for ring formation passes through a minimum

¹ E. G. E. Hawkins, "Organic Peroxides: Their Formation and Reactions," p. 229. Spon, London, 1961.

² A. Rieche, "Alkylperoxyde und Ozonide," Steinkopff, Dresden, 1931.

³ R. Criegee, *Fortschr. Chem. Forsch.* **1**, 508 (1950).

⁴ R. Criegee, in "Methoden der organischen Chemie," Houben-Weyl's 4th ed., Vol. 8, p. 1. Thieme, Stuttgart, 1952.

⁵ A. G. Davies, "Organic Peroxides." Butterworth, London and Washington, D.C., 1961.

⁶ W. O. Lundberg, "Autoxidation and Antioxidants." Wiley (Interscience), New York, 1961.

⁷ A. V. Tobolsky and R. B. Mesrobian, "Organic Peroxides; Their Chemistry, Decomposition and Role in Polymerisation." Wiley (Interscience), New York, 1954.

⁸ P. S. Bailey, *Chem. Rev.* **58**, 925 (1958).

⁹ A. Étienne, in "Traité de Chimie Organique" (V. Grignard *et al.*, eds.), Vol. 17, p. 1299, 1949.

¹⁰ K. Gollnick and G. O. Schenck, in "1,4-Cycloaddition Reactions: The Diels-Alder Reaction in Heterocyclic Syntheses" (J. Hamer, ed.), p. 255. Academic Press, New York, 1966.

¹¹ R. S. Porter and G. H. Cady, *J. Am. Chem. Soc.* **79**, 5228 and 5625 (1957).

¹² R. L. Talbott, *J. Org. Chem.* **30**, 1429 (1965); J. H. Prager *J. Org. Chem.*, **31**, 392 (1966).

¹³ H. L. Roberts, *J. Chem. Soc.* p. 4538 (1964).

¹⁴ R. Hiatt and T. G. Traylor, *J. Am. Chem. Soc.* **87**, 3768 (1965).

with medium-sized rings in the carbocyclic series,¹⁵ medium-sized peroxidic rings can be formed surprisingly easily.¹⁶ The reason for this appears to be that the replacement of CH₂ groups by oxygen^{17, 18} leads to a considerable decrease in ring strain (Pitzer strain), and so favors the formation of seven to ten-membered peroxide rings.

No three- or four-membered peroxide rings are known at present. Though stable peroxides were often formulated as three- or four-membered rings in the older literature,^{1, 3} detailed examination always showed that the structure was actually different.

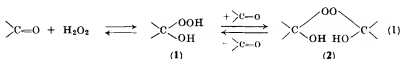
Small peroxide rings probably merit more attention as short-lived intermediates. However, though they have often been postulated in this capacity, they have never been detected.

II. Syntheses of Cyclic Peroxides with Hydrogen Peroxide

A. CYCLIC PEROXIDES OF CARBONYL COMPOUNDS

1. From Ketones and Aldehydes

The first products of the reaction of hydrogen peroxide with carbonyl compounds are α -hydroxyalkyl hydroperoxides (1) and dihydroxydialkyl peroxides (2) [Eq. (1)].^{2, 19}



In the presence of mineral acids, the hydroxyl groups in 1 and 2 can be readily replaced by —OOH, —OOR, or —OR. The substitutions can also take place intramolecularly, in which case the products are cyclic peroxides. The substitution of the OH group is favored by the formation of the resonance-stabilized cation (3) as an intermediate.²⁰

Depending on reaction conditions, such as the hydrogen peroxide concentration and the acid concentration, 2 reacts with hydrogen

¹⁵ R. Huisgen, *Angew. Chem.* **69**, 341 (1957).

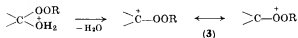
¹⁶ R. Criegee, W. Schnorrenberg and J. Becke, *Ann.* **565**, 7 (1949).

¹⁷ K. Ziegler and H. Holl, *Ann.* **528**, 143 (1937).

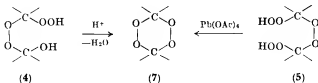
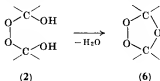
¹⁸ K. Ziegler, in "Methoden der organischen Chemie," Houben-Weyl's 4th ed., Vol. 4, Pt. 2, p. 735. Thieme, Stuttgart, 1955.

¹⁹ For a review of earlier works, see: A. Rieche, *Angew. Chem.* **70**, 251 (1958).

²⁰ A. Rieche, *Angew. Chem.* **73**, 57 (1961).



peroxide to give either a hydroxyhydroperoxydialkyl peroxide (4) or the bis(hydroperoxy)dialkyl peroxide (5).^{16, 20, 21}



The intramolecular elimination of water from 2 with phosphorus pentoxide²² yields 1,2,4-trioxolans (6)²²⁻²⁴ (Rieche's "ozonide synthesis without ozone"²²).

Intramolecular elimination of water from 4 leads to cyclic peroxides with two peroxy groups in one six-membered ring (1,2,4,5-tetroxans) (7). This reaction generally requires the use of strong mineral acids (concentrated sulfuric acid,²⁵ perchloric acid²⁶) or P_4O_{10} .²⁵ 4 underwent cyclization to give 7 when heated in glacial acetic acid.²⁷ 1,2,4,5-

²¹ N. A. Milas, S. A. Harris, and P. S. Panagiotakos, *J. Am. Chem. Soc.* **61**, 2430 (1939).

²² A. Rieche and R. Meister, *Ber.* **65**, 1274 (1932).

²³ A. Rieche, R. Meister, and H. Sauthoff, *Ann.* **553**, 187 (1942).

²⁴ R. Criegee and G. Lohaus, *Ber.* **86**, 1 (1953).

²⁵ W. Cooper, *J. Chem. Soc.* p. 1340 (1951).

²⁶ M. S. Kharasch and G. Sosnovsky, *J. Org. Chem.* **23**, 1322 (1958).

²⁷ A. Rieche and C. Bischoff, *Ber.* **95**, 77 (1962).

Tetroxans ("dimeric ketone or aldehyde peroxides") (7) are readily obtainable from carbonyl compounds and Caro's acid or hydrogen peroxide and sulfuric acid by the method described by Baeyer and Villiger.^{28, 29} However, aromatic ketones undergo a Baeyer-Villiger rearrangement under these conditions to form esters of carboxylic acids.³⁰

Thus, reactions of carbonyl compounds with hydrogen peroxide and acids lead to products similar to those obtained by the ozonization of olefins (Section III), which also yields 1,2,4-trioxolans and 1,2,4,5-tetroxans. The similarity of the two reactions is understandable, since the intermediates $\text{>C}^+-\text{OO}^-$ in the ozonization^{27a} and $\text{>C}^+-\text{OOH}$ in the hydrogen peroxide reactions are related as a conjugate base-acid pair. A number of cyclic peroxides of structure 7 are prepared from bis(hydroperoxy)dialkyl peroxides (5) by reaction with lead(IV) acetate, as described by Criegee *et al.*¹⁶ This reaction is also thought to involve a carbonium ion intermediate,³¹ which reacts with the second OOH group.

Hydrogen peroxide reactions are often transacetalizations, as is shown by the formation of the "dimeric ethylidene peroxide" (11) from sulfuryl chloride, hydrogen peroxide, and ether.³² This reaction probably involves the α -chloroether (8), the ether hydroperoxide (9), and the cation (10) as intermediates.

The formation of 11 in the autoxidation of diethyl ether^{19, 33} also proceeds via the hydroperoxide (9), which preferentially splits off the alkoxy group.

On reaction with iodide in acidic media, 3,6-dimethyl-1,2,4,5-tetroxan (11) gives only one tenth of the calculated iodine equivalent.³⁴ The reduction is evidently subject to competition by decomposition of the protonated peroxide as indicated in 12.

Reaction of the bis(hydroperoxy)dialkyl peroxides (5) with car-

^{27a} The carbonyl oxide structure is usually drawn as $\text{C}^+=\text{O}-\text{O}^-$, and so this structure will be most generally used in this chapter. In our opinion, however, $\text{C}=\text{O}^+-\text{O}^-$, with its smaller charge separation and carbon electron octet, is preferable.

²⁸ A. Baeyer and V. Villiger, *Ber.* **32**, 3625 (1899).

²⁹ A. Baeyer and V. Villiger, *Ber.* **33**, 2479 (1900).

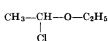
³⁰ C. H. Hassall, *Org. Reactions* **9**, 73.

³¹ H. Hoek and H. Kropf, *Ber.* **91**, 1681 (1958).

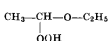
³² M. Schmidt and P. Bornmann, *Z. Naturforsch.* **19b**, 536 (1964).

³³ A. Rieche and R. Meister, *Angew. Chem.* **49**, 101 (1936).

³⁴ A. Rieche and R. Meister, *Ber.* **72**, 1933 (1939).



(8)



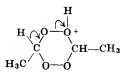
(9)



(10)

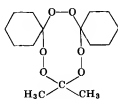


(11)



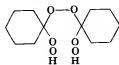
(12)

bonyl compounds (particularly ketones) in the presence of copper sulfate and strong mineral acid leads to elimination of water and formation of nine-membered ring peroxides. Criegee *et al.*¹⁶ obtained the cyclic peroxides (13 and 14) by this method, and proved the structure of the "trimeric acetone peroxide" (15) by synthesis.

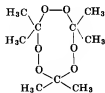


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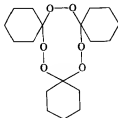
Acetone



Cyclohexanone



(15)



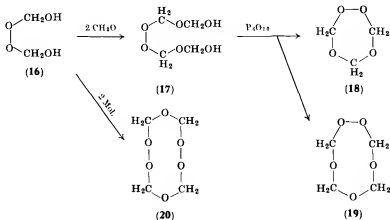
(14)

Whereas "dimeric ketone peroxides" (7) liberate the equivalent quantity of iodine when heated with acidic potassium iodide solution, "trimeric ketone peroxides" (13, 14, and 15) do not react quantitatively with iodide.¹⁶ The same behavior of the two types of ketone

peroxides is observed on catalytic hydrogenation.¹⁶ The stability of the nine-membered ring peroxides is due to steric effects.

While the reaction of ketones with hydrogen peroxide yields only six- and nine-membered ring peroxides, other peroxidic ring structures are formed from aldehydes. From formaldehyde and hydrogen peroxide, for example, Rieche and Meister³⁵ obtained cyclic peroxides with seven-, nine-, and ten-membered rings.

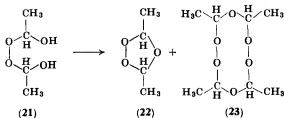
Bis(hydroxymethyl) peroxide (16), the adduct of 2 moles of formaldehyde and 1 mole of hydrogen peroxide, reacts with monomeric formaldehyde to give the dimethylol compound (17), which is converted by treatment with P_4O_{10} into a mixture of the seven-membered ring peroxide (18) (principal product) and the nine-membered ring peroxide (19). A notable reaction is the formation of the crystalline, highly explosive ten-membered ring peroxide (20) ("dimeric ethylene ozonide") from 16 by elimination of water with P_4O_{10} .



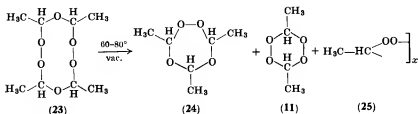
Rieche and Meister³⁴ obtained bis(1-hydroxyethyl) peroxide (21) from 2 moles of acetaldehyde and 1 mole of hydrogen peroxide. Treatment of 21 with phosphorus pentoxide in ether followed by distillation gives 3,5-dimethyl-1,2,4-trioxolan (2,3-butylene ozonide) (22) as the distillate and "dimeric butylene ozonide" with a ten-membered ring structure (23) as the residue.^{23, 34}

Thermal decomposition of (23) at 60 to 80° *in vacuo* yields polymeric ethylidene peroxide (25), 3,5,7-trimethyl-1,2,4,6-tetroxepan (mono-

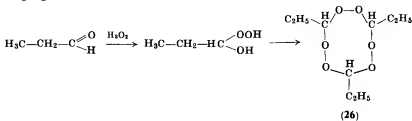
³⁵ A. Rieche and R. Meister, *Ber.* **66**, 718 (1933).



perparaldehyde (24), and the highly explosive "dimeric ethylidene peroxide" (3,6-dimethyl-1,2,4,5-tetroxan) (11).³⁴ 25 was also detected in the residues from autoxidized diethyl ether, and is the cause of their explosive character.¹⁹ On hydrolysis of "dimeric butylene ozonide" (23) with dilute sulfuric acid, 80% of the theoretical quantity of hydrogen peroxide was liberated, while alkaline hydrolysis of 23 yields 2 moles of acetic acid.²³



α -Hydroxypropyl hydroperoxide, which is obtained from propionaldehyde and hydrogen peroxide, reacts with P_4O_{10} in ether to form an oil, which must, on the basis of analysis and molecular weight determination, be a nine-membered ring peroxide (26) with three peroxy groups. This compound is isomeric with "trimeric acetone peroxide" (15), and is the only known "trimeric aldehyde peroxide." 26 reacts with 0.1 N sodium hydroxide solution to give a 74% yield of propionic acid.³⁶

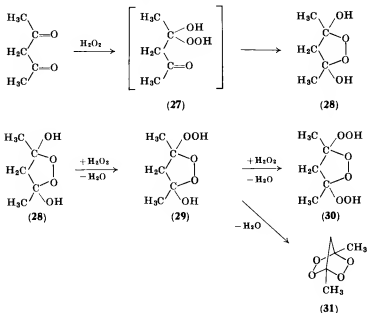


³⁶ A. Rieche and R. Meister, *Ber.* **72**, 1938 (1939).

2. From Diketones and Dialdehydes

Cyclic peroxides are obtained from diketones when a five- or six-membered peroxide ring can be formed, as is the case with acetylacetone, acetonylacetone, triacetylmethane, and benzalacetylacetone. In the reaction of 1,2-diketones with hydrogen peroxide, the C—C bond is broken to give carboxylic acids, without intermediate formation of a four-membered peroxide ring.³⁷

Rieche and Bischoff²⁷ reported the formation of cyclic peroxides of acetylacetone. Hydrogen peroxide first adds to one carbonyl group. The hydroxyhydroperoxide (27) cannot be isolated, but reacts further to form the five-membered ring peroxide (28), which crystallizes well. Under slightly modified reaction conditions, the hydroxyl groups in 28 are replaced by hydroperoxy groups to give the crystalline hydroperoxy-1,2-dioxolans (29 and 30); the latter readily forms a bis-*p*-nitrobenzoate.³⁸ When heated in glacial acetic acid²⁷ or with P₄O₁₀

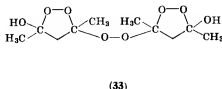
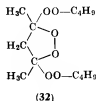


²⁷ J. E. Leffler, *J. Org. Chem.* **16**, 1785 (1951).

³⁸ N. A. Milas, O. L. Mageli, A. Golubović, R. W. Arndt, and J. C. J. Ho, *J. Am. Chem. Soc.* **85**, 222 (1963).

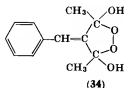
in ether,³⁸ **29** loses 1 mole of water to form the crystalline 1,2,4,5-tetroxan (**31**) with an endomethylene bridge. **31**, like "dimeric ethylidene peroxide" (**11**), is highly explosive and sensitive to friction.

In the presence of mineral acids, the OH groups of **28** can also be replaced by *tert*-butylperoxy groups to give **32**.²⁷ The bis-1,2-dioxolanyl-(3)-peroxide (**33**) has been obtained in small yield as a by-product in the reaction of acetylacetone with hydrogen peroxide.²⁷



Milas *et al.*³⁸ carried out NMR spectroscopic studies in which they found that **28** exists in solution as a 2:3 mixture of the *cis* and *trans* isomers. **29** and **30** exist only as the *trans* isomers. The symmetrical bicyclic peroxide (**31**) may be considered as a derivative of the *cis* form, the corresponding *trans* isomer being incapable of existence, because of the steric factor. The course of the formation of the cyclic peroxides **28** to **31** has been followed by UV spectroscopy.³⁸

The addition of hydrogen peroxide to benzalacetylacetone yields the dioxolan derivative (**34**).²⁷

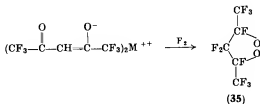


The thermal decomposition of 3,5-dihydroxy-3,5-dimethyl-1,2-dioxolan (**28**) in glacial acetic acid or water at 110° is very complex, and leads to the following products: acetic acid (60%), lactic acid (13%), propionic acid (6%), carbon dioxide (6%), acetylacetone (10%), methane (5%), carbon monoxide (2%), formic acid (1%), 3,5-diacetylheptane-2,6-dione (0.4%), and a mixture of acetone, methyl ethyl ketone, acetaldehyde, and methylglyoxal.^{39, 40}

³⁹ A. Rieche and C. Bischoff, *Ber.* **96**, 2607 (1963).

⁴⁰ C. Bischoff, *Monatsber. Deut. Akad. Wiss. Berlin* **6**, 252 (1964).

Talbott¹² obtained the fluorinated 1,2-dioxolan (**35**) by treatment of the copper(II) or nickel(II) chelate of hexafluoroacetylacetone with fluorine at -20° .



This is one of the rare cases of "spontaneous generation" of a peroxide bond from oxygen fragments. The structure of **35** is confirmed by IR and NMR spectra. The F^{19} -NMR spectrum shows that the compound exists mainly in the *trans* form. The *cis* compound is less stable than the *trans* isomer, more than 50% of the *cis* isomer having decomposed within 3 days, whereas the *trans* isomer had not decomposed. The decomposition of **35** yields difluorocarbene.

Cyclic peroxides with six-membered rings are obtained from acetylacetone and hydrogen peroxide.^{41, 42} Rieche *et al.*⁴¹ obtained the 1,2-dioxolan derivative (**36**) (85%), and replacement of the hydroxyl groups in **36** with $-\text{OOH}$ leads to **37**.



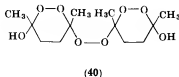
Milas and Golubovic⁴² used paper and column chromatography and spectroscopic methods to study the reaction of acetylacetone with hydrogen peroxide. Beside compound **37**, a peroxide (**38**) with the tetrahydrofuran structure is also reported to be formed.⁴² Seebach⁴³ also obtained **37** from 2,5-dimethylfuran, 85% hydrogen peroxide, and a little 10% sulfuric acid (see Section II, A, 5). **37** forms a dibenzoate.⁴³

⁴¹ A. Rieche, C. Bischoff, and M. Pulz, *Ber.* **95**, 2005 (1962).

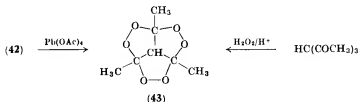
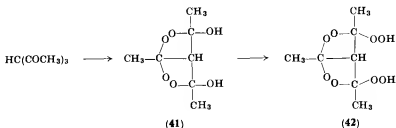
⁴² N. A. Milas and A. Golubovic, *J. Org. Chem.* **27**, 4319 (1962).

⁴³ D. Seebach, *Ber.* **96**, 2712 (1963).

On reaction with hydrogen peroxide, acetylacetone tends to form polymeric peroxides, for which structure **39** is proposed. A dimeric 1,2-dioxanyl peroxide (**40**) has also been described.⁴¹



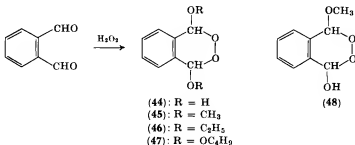
Bicyclic and tricyclic peroxides were obtained by Rieche *et al.*⁴⁴ from triacetyl methane and hydrogen peroxide. The first isolable reaction product is the bicyclic compound (**41**), in which one or both hydroxyl groups can be replaced by hydroperoxy groups (**42**).



The tricyclic peroxide (**43**) ("triacetyl methane peroxide") is formed (yield ~20%) in an exothermic reaction when 80% sulfuric acid is added to a mixture of triacetyl methane and 40% hydrogen peroxide. The tricyclic structure is proved by the conversion of **42** into **43** on reaction with lead tetraacetate. In agreement with structure **43**, the NMR spectrum contains two sharp singlets at $\tau = 8.35$ and $\tau = 5.98$.⁴⁴

⁴⁴ A. Rieche, C. Bischoff, and D. Prescher, *Ber.* **97**, 3071 (1964).

By reaction of *o*-phthaldialdehyde with ethereal hydrogen peroxide in the presence of a little mineral acid, Rieche and Schulz⁴⁵ obtained the six-membered ring peroxide (**44**), which crystallizes out after a short reaction time.



In the presence of mineral acids, the hydroxyl groups in **44** can be replaced by alkoxy or alkylperoxy groups to give **45**, **46**, or **47**. The monomethoxy compound (**48**) occurs as an intermediate in the formation of the dimethoxy compound (**45**). **48** was obtained by Bailey *et al.*⁴⁶ on ozonization of naphthalene, 2-methoxynaphthalene, and 2-ethoxynaphthalene in methanol. Ozonization of 2-ethoxynaphthalene in ethanol leads to the diethoxy compound (**46**).⁴⁶ The peroxides **44–46** and **48** can be converted into *o*-phthaldialdehyde (in 55% yield from **48**) by hydrogenation in the presence of a Lindlar catalyst.⁴⁵ The peroxide oxygen in **45–48** cannot be quantitatively determined by iodometry.⁴⁵

3. From α,β -Unsaturated Ketones

Mesityl oxide and hydrogen peroxide react to form a crystalline peroxide, which was prepared by Wolffenstein⁴⁷ as early as 1895. In 1939 Rieche² expressed doubts regarding the formula originally proposed for this compound, but it was only in 1959 that Rieche *et al.*⁴⁸ were able to elucidate its structure.

The first step is probably the addition of hydrogen peroxide to the C—C double bond, since conjugated unsaturated ketones are very difficult to ketalize.⁴⁹ The intermediate hydroperoxyketone (**49**)

⁴⁵ A. Rieche and M. Schulz, *Ber.* **97**, 190 (1964).

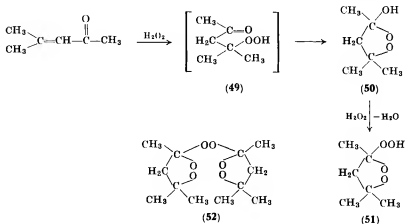
⁴⁶ P. S. Bailey, S. S. Bath, F. Dobinson, F. J. Garcia-Sharp, and C. D. Johnson, *J. Org. Chem.* **29**, 697 (1964).

⁴⁷ R. Wolffenstein, *Ber.* **28**, 2265 (1895).

⁴⁸ A. Rieche, E. Schmitz, and E. Gründemann, *Ber.* **93**, 2443 (1960).

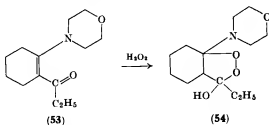
⁴⁹ F. Strauss, *Ann.* **458**, 257 (1927).

undergoes intramolecular ketalization to form the hydroxy-1,2-dioxolan (50). This was first obtained by Payne⁵⁰ as a by-product in the alkaline epoxidation of mesityl oxide with hydrogen peroxide.



50 reacts with hydrogen peroxide to form the hydroperoxydioxolan (51). Treatment of 51 or 50 with hydrogen peroxide in acidic media leads to "mesityl oxide peroxide" (52).⁴⁸

Rieche *et al.*⁵¹ report (without giving experimental details) that the enamine ketone (53) is converted by hydrogen peroxide into the cyclic peroxide (54). The principle of this reaction is the same as that of the reaction of mesityl oxide with hydrogen peroxide.



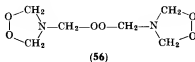
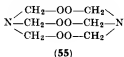
4. From Carbonyl Compounds and Amines

The first report of a heterocycle containing nitrogen in the ring as well as peroxide groups appeared in the literature in 1900. Baeyer and

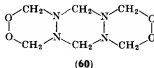
⁵⁰ G. B. Payne, *J. Org. Chem.* **23**, 310 (1958).

⁵¹ A. Rieche, E. Schmitz, and E. Gründemann, *Angew. Chem.* **72**, 635 (1960).

Villiger²⁹ allowed ammonia, formaldehyde, and hydrogen peroxide to react in weakly acidic solution, and obtained a crystalline, explosive peroxide, to which they assigned the structure **55**. Girsewald and Siegens⁵² later proposed structure **56** for the same compound. Marotta and Alessandrini⁵³ and Schmitz⁵⁴ examined the two structures (**55** and **56**), and decided in favor of the Baeyer-Villiger formula (**55**).



Girsewald and Siegens⁵² reacted hydrazine, formaldehyde, and hydrogen peroxide in weakly acidic solution, and obtained a peroxide for which they gave the structure **57**.



The same heterocycle was thought to be the basis of compounds **58** and **59** obtained from ethylamine and from urea with formaldehyde and hydrogen peroxide. However, the reported solubilities of the peroxides **57**, **58**, and **59** later gave rise to doubt regarding the correctness of the structures proposed.⁵⁵ On the basis of molecular weight determinations on the product thought by Girsewald and Siegens⁵² to have structure **57**, Schmitz⁵⁶ proposed a structure **60** with a hexahydrotetrazine ring in the middle, to which two six-membered peroxide rings are fused. Similarly the structures of the peroxides obtained from ethylamine and urea with formaldehyde and hydrogen peroxide do not correspond to the formulae **58** and **59**. These products are, in fact, linear condensed peroxides with high molecular weights.^{54, 56}

⁵² C. von Girsewald and H. Siegens, *Ber.* **54**, 492 (1921).

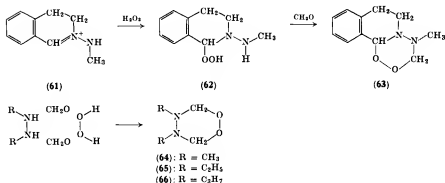
⁵³ D. Marotta and M. E. Alessandrini, *Gazz. Chim. Ital.* **59**, 942 (1929).

⁵⁴ E. Schmitz, Habilitationsschrift Math.-Nat. Fakultät, Humboldt-Universität, Berlin, p. 68 (1959).

⁵⁵ R. Criegee, in "Methoden der organischen Chemie," Houben-Weyls 4th ed., vol. 8, p. 59. Thieme, Stuttgart, 1952.

⁵⁶ E. Schmitz, *Ann.* **635**, 73 (1960).

Schmitz⁵⁶ was able to synthesize a number of compounds containing the 1,2-dioxatetrahydropyridazine ring found in **60**. The peroxide (**63**) is obtained by reaction of the immonium salt (**61**) with formaldehyde and hydrogen peroxide, probably via the hydroperoxide (**62**). 1,2-Dialkylhydrazines can be condensed with formaldehyde and hydrogen peroxide under carefully controlled conditions to give 1,2-dioxatetrahydropyridazines (**64**, **65**, and **66**).⁵⁶



These peroxides are not very stable, owing to the presence of a readily oxidizable aliphatic hydrazine grouping and a strong oxidizing group (the peroxide group) in the same ring. **65** decomposes at room temperature in ethanol or benzene to form 1 mole of azoethane and 2 moles of formaldehyde, the rates of decomposition in the two solvents being approximately the same.⁵⁷

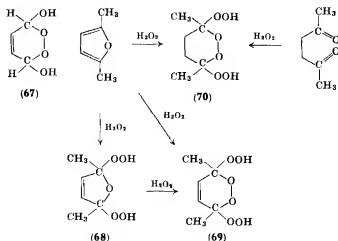
5. Other Routes to Cyclic Peroxides from Carbonyl Compounds

Furan reacts with hydrogen peroxide to give the unstable cyclic peroxide (**67**), which forms maleic dialdehyde on hydrogenation.⁵⁸ Seebach⁴³ obtained a mixture of stable cyclic peroxides from 2,5-dimethylfuran and hydrogen peroxide. In addition to 2,5-dihydroperoxy-2,5-dimethyldihydrofuran (**68**), the six-membered ring peroxides **69** and **70** are also formed; **70** has already been described as resulting from the action of hydrogen peroxide on acetylacetone.^{41, 42}

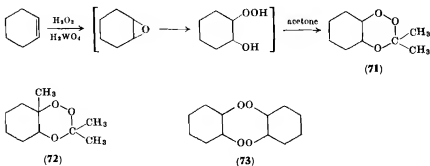
⁵⁷ A. Rieche, E. Schmitz, and A. Stark, private communication by E. Schmitz, 1966.

⁵⁸ N. A. Milas, R. L. Peeler, Jr., and O. L. Mageli, *J. Am. Chem. Soc.* **76**, 2322 (1954).

Treatment of **68** with hydrogen peroxide in the presence of a little sulfuric acid yields the highly explosive dimethyldioxene derivative (**69**).



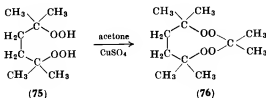
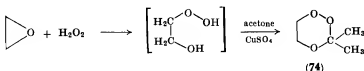
Payne and Smith⁵⁹ studied the hydroxylation of cyclohexene with a mixture of 34% hydrogen peroxide and a little tungstic acid in acetone. In addition to *trans*-1,2-cyclohexanediol, they obtained a 25% yield of 3,3-dimethyl-1,2,4-trioxa-*trans*-decalin (**71**), which may be regarded as the "acetone derivative" of the intermediate β -hydroxyhydroperoxide. Hydrogenation of **71** leads to *trans*-cyclohexane-1,2-diol.



⁵⁹ G. B. Payne and C. W. Smith, *J. Org. Chem.* **22**, 1682 (1957).

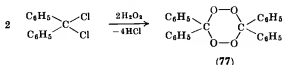
The 1,2,4-trioxan derivative (**72**) was obtained by a similar method from 1-methylcyclohexene.⁶⁰ Treatment of **71** with 25% perchloric acid at 0° is reported to lead to an 88% yield of the crystalline eight-membered ring peroxide (**73**). Structure **73** is based on analytical and IR spectroscopic evidence and on the molecular weight; catalytic hydrogenation leads to *trans*-cyclohexane-1,2-diol.

By reaction of ethylene oxide with hydrogen peroxide and acetone, Schulz⁶¹ obtained the remarkably stable 3,3-dimethyl-1,2,4-trioxan (**74**) in the form of a liquid (b.p. = 48–51°/31 mm, n_D^{20} = 1.4191).



Criegee *et al.*¹⁶ converted the bishydroperoxide (**75**) into the cyclic peroxide (**76**), which is isosteric with "trimeric acetone peroxide," by reaction with acetone in the presence of copper sulfate as a condensing agent.

Another route to cyclic peroxides from carbonyl compounds is illustrated by the reaction of dichlorodiphenylmethane with hydrogen peroxide to form the dimeric benzophenone peroxide (**77**),⁶² which reacts with zinc in acetic acid to form benzopinacolone ($\text{Ph}_2\text{C}=\text{CO}-\text{Ph}$), and with aluminum amalgam to form benzhydrol. On fusion (183–225°), **77** decomposes to form benzophenone.



⁶⁰ F. Nittel, Dissertation, Technische Hochschule Karlsruhe, 1961.

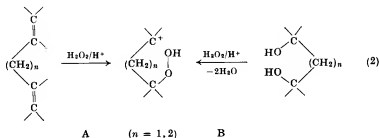
⁶¹ M. Schulz, unpublished material, 1966.

⁶² C. S. Marvel and V. E. Nichols, *J. Am. Chem. Soc.* **60**, 1455 (1938).

B. CYCLIC DIALKYL PEROXIDES

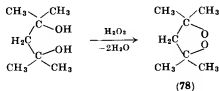
Only a few cyclic dialkyl peroxides have been prepared by reaction with hydrogen peroxide. The large class formed by the endoperoxides, most of which are prepared by diene synthesis with oxygen, is discussed in Section IV.

There are two conceivable routes [A and B, Eq. (2)] for the synthesis of dialkyl peroxides with hydrogen peroxide.

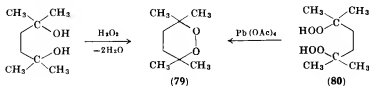


There are at present no known examples of intramolecular alkylation of ROOH by route A.

Criegee and Paulig⁶³ obtained the substituted 1,2-dioxolan (78) in 31% yield by reaction of 2,4-dimethylpentane-2,4-diol with 80% hydrogen peroxide (route B).



The homologous 1,4-glycol reacts at 60 to 65°, though only in the presence of strong sulfuric acid, to give a 28% yield of the six-membered ring peroxide (79).⁶³



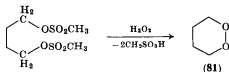
⁶³ R. Criegee and G. Paulig, *Ber.* **88**, 712 (1955).

If the reaction time is too short, the bishydroperoxide (**80**) is isolated. This can be cyclized with lead tetraacetate to give **79**.

78 and **79** are very stable peroxides, which can be distilled in small quantities even at normal pressure. On reaction with sodium iodide in glacial acetic acid, iodine separates out more rapidly with **78** than with **79**. The UV spectra, as with other peroxides, are not very characteristic,^{23, 64} and the spectrum of **79** is almost identical with that of simple ozonides.⁶⁴

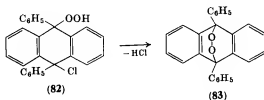
NMR spectroscopy shows that **79** has a chair structure. At temperatures below +3°, the axial and equatorial methyl groups give separate signals.^{65, 66}

Criegee and Müller⁶⁷ obtained unsubstituted 1,2-dioxan (**81**) in 30% yield from butandiol-1,4-bismethanesulfonate and hydrogen peroxide by the method described by Welch *et al.*⁶⁸ The pH must be strictly controlled in this synthesis.



The peroxide oxygen in **81** can be detected with 57% hydriodic acid and glacial acetic acid only after being heated. Hydrogenation of **81** leads to butane-1,4-diol, while decomposition with acids or bases leads to γ -hydroxybutyraldehyde.⁶⁷

Pinazzi⁶⁹ obtained "diphenylanthracene peroxide" (**83**) by the intramolecular alkylation of the hydroperoxide (**82**) with alkali.



⁶⁴ R. Criegee, *Ann.* **583**, 1 (1953).

⁶⁵ H. Friebolin and W. Maier, *Z. Naturforsch.* **16a**, 640 (1961).

⁶⁶ G. Claison, G. Androes, and M. Calvin, *J. Am. Chem. Soc.* **83**, 4357 (1961).

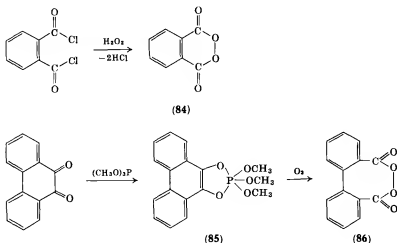
⁶⁷ R. Criegee and G. Müller, *Ber.* **89**, 238 (1956).

⁶⁸ F. Welch, H. R. Williams, and H. S. Mosher, *J. Am. Chem. Soc.* **77**, 551 (1955).

⁶⁹ C. Pinazzi, *Compt. Rend.* **226**, 929 (1948).

C. CYCLIC DIACYL PEROXIDES

Though many open-chain diacyl peroxides have been described, very few cyclic compounds of this type are known. Monomeric cyclic phthaloyl peroxide (**84**) is prepared by treatment of phthaloyl chloride in chloroform with aqueous sodium peroxide solution in the presence of phosphate buffer, or by reaction of phthaloyl chloride with ethereal hydrogen peroxide in the presence of sodium carbonate.⁷⁰⁻⁷² Russell⁷¹ has also obtained cyclic diacyl peroxides from the dichlorides of the C₁₀, C₁₂, and C₁₄ dicarboxylic acids. Only polymeric diacyl peroxides were obtained from lower dicarboxylic acids.



Another route to cyclic diacyl peroxides was discovered by Ramirez *et al.*⁷³ A mixture of phenanthraquinone and trimethyl phosphite in methylene chloride gives an adduct (**85**) at room temperature, and this adduct is ozonized at -70° . Diphenoyl peroxide (**86**) is formed in 50% yield.

Iodine is liberated quantitatively from acidic iodide solution by **84** and **86**.⁷¹⁻⁷³ Reduction of the cyclic diphenoyl peroxide (**86**) with triphenylphosphine or trimethyl phosphite leads to an 80% yield of

⁷⁰ H. Kleinfeller and K. Rastädter, *Angew. Chem.* **65**, 543 (1953).

⁷¹ K. E. Russell, *J. Am. Chem. Soc.* **77**, 4814 (1955); *Canad. J. Chem.* **38**, 1600 (1960).

⁷² F. D. Greene, *J. Am. Chem. Soc.* **78**, 2246 (1956).

⁷³ F. Ramirez, N. B. Desai, and R. B. Mitra, *J. Am. Chem. Soc.* **83**, 492 (1961).

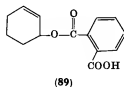
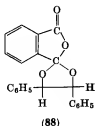
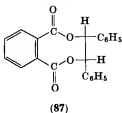
2,2'-diphenic anhydride, while the reduction of cyclic phthaloyl peroxide with triphenylphosphine leads to quantitative formation of phthalic anhydride.⁷⁴ Thioethers are quantitatively oxidized to sulfoxides or sulfones by **84**.⁷⁴ The oxidation proceeds more readily than with open-chain diacyl peroxides; this is due to ring strain.

The decomposition of **84** in dimethylaniline was studied by Horner and Brüggemann.⁷⁴ Greene has published a number of papers on the chemical behavior of the cyclic phthaloyl peroxide (**84**).^{72, 75-79}

Decomposition of **84** in benzene at 80° yields *o*-phenylbenzoic acid (50%), polymeric acid (25%), phthalic acid (7%), benzoic acid (5%), carbon dioxide (78%), and a little 3,4-benzocoumarin and diphenyl.⁷² The first step in this induced decomposition is homolytic cleavage of the peroxide bond.⁷²

Cyclic phthaloyl peroxide (**84**) reacts with olefins in bimolecular, nonradical reactions, which are first order with respect to peroxide and olefin.⁷⁸ These reactions begin with an electrophilic attack on the double bond by the peroxide.

The agreement of the relative reaction rate with those found for other double-bond reagents, such as peracetic acid, dibromocarbene, and bromine, is remarkable.⁷⁶ A stereospecific reaction takes place in the cases of *cis*- and *trans*-stilbenes. Phthaloyl peroxide in which the carbonyl oxygen is labeled with O¹⁸ was also considered in the course of these investigations.⁷⁷ The reaction of *trans*-stilbene in boiling carbon tetrachloride leads to the cyclic phthalate of *dl*-hydrobenzoin (**87**) and the lactonic ortho ester (**88**), while *cis*-stilbene gives the corresponding meso compounds.⁷⁵ Olefins with hydrogen atoms in



⁷⁴ L. Horner and H. Brüggemann, *Ann.* **635**, 22 (1960).

⁷⁵ F. D. Greene, *J. Am. Chem. Soc.* **78**, 2250 (1956).

⁷⁶ F. D. Greene and W. W. Rees, *J. Am. Chem. Soc.* **80**, 3432 (1958).

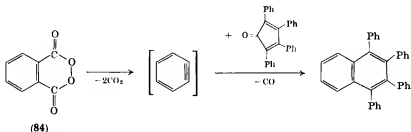
⁷⁷ F. D. Greene, *J. Am. Chem. Soc.* **81**, 1503 (1959).

⁷⁸ F. D. Greene and W. W. Rees, *J. Am. Chem. Soc.* **82**, 890 (1960).

⁷⁹ F. D. Greene and W. W. Rees, *J. Am. Chem. Soc.* **82**, 893 (1960).

the allyl position do not undergo stereospecific addition with **84**; cyclohexene gives 3-cyclohexenyl hydrogen phthalate (**89**).⁷⁶ Diaryl-acetylene reacts with 2 moles of cyclic phthaloyl peroxide (**84**).⁷⁹

Greene⁷² and Horner and Brüggemann⁷⁴ suggested that the photolysis of **84** might lead to the formation of dehydrobenzene, and this product was detected by Wittig and Ebel^{80, 81} on photolysis of **84** in the presence of tetracyclone. The benzyne formed as an intermediate reacts with the tetracyclone to form tetraphenylnaphthalene (7.4%).

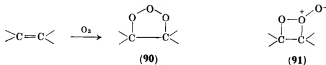


III. Syntheses of Cyclic Peroxides with Ozone

A. OZONIZATION MECHANISM

The ozonization of olefins yields not only the ozonides (which were first isolated by Harries,⁸² and whose structures were subsequently elucidated by Staudinger⁸³ and Rieche),^{2, 23} but also other cyclic peroxides. The formation of these products is explained by the ozonization mechanism proposed by R. Criegee⁶⁴ In 1958, Bailey⁸ published a review of ozonization reactions in general.

Ozone first reacts with the olefin to form a primary ozonide, which probably has the five-membered ring (1,2,3-trioxolan) structure (**90**) as a result of a 1,3 dipolar addition.⁸⁴



⁸⁰ G. Wittig and H. F. Ebel, *Ann.* **650**, 20 (1961).

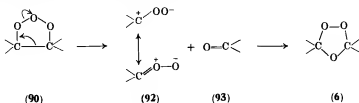
⁸¹ G. Wittig, *Angew. Chem.* **74**, 483 (1962).

⁸² C. Harries, *Ann.* **343**, 311 (1905); **374**, 288 (1910); **390**, 236 (1912); **410**, 1 (1915).

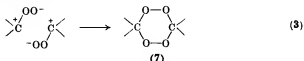
⁸³ H. Staudinger, *Ber.* **58**, 1088 (1925).

⁸⁴ R. Huisgen, *Angew. Chem.* **75**, 604 (1963); see also P. S. Bailey, J. A. Thompson, and B. A. Shoulders, *J. Am. Chem. Soc.* **88**, 4098 (1966).

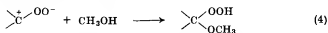
A four-membered ring structure (91) has also been proposed for the primary ozonide, but this seems unlikely in view of the appreciable strain that should be present in four-membered ring structures.⁸⁴ 90 decomposes readily into the peroxidic zwitterion⁸⁴ (carbonyl oxide⁸⁴) (92) and a carbonyl fragment (93).^{84a}



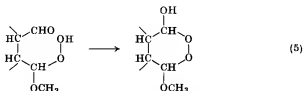
It is the recombination of these fragments, again by 1,3-dipolar addition, that finally leads to the true ozonide (1,2,4-trioxolane) (6). The zwitterion (92) is of primary importance in the ozonization process. 1,2,4,5-Tetroxans ("dimeric alkylidene peroxides") (7) are formed by their dimerization [Eq. (3)].^{85, 86}



Ozonolysis of an olefin in a solvent containing hydroxyl groups (e.g., methanol) does not lead to either 6 or 7, but results in addition of the solvent to 92.^{84, 85, 87} The addition of methanol leads to α -methoxyhydroperoxides [Eq. (4)].



The OOH group in the hydroperoxides formed in accordance with Eq. (4) can react with a carbonyl group in the same molecule [carbonyl fragment (93)] to give ring closure [Eq. (5)].



^{84a} For a new discussion of the ozonization mechanism, see P. R. Story, R. W. Murray, and R. D. Youssefeyeh, *J. Am. Chem. Soc.* **88**, 3144 (1966).

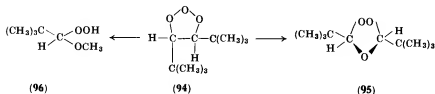
⁸⁵ R. Criegee and G. Wenner, *Ann.* **564**, 9 (1949).

⁸⁶ R. Criegee and G. Lohaus, *Ann.* **583**, 6 (1953).

⁸⁷ A. Rieche, M. Schulz, and D. Becker, *Ber.* **98**, 3627 (1965).

B. PRIMARY OZONIDES AND ADDUCTS OF OZONE
WITH AROMATIC COMPOUNDS

Criegee and Schröder⁸⁸ obtained the first primary ozonide (**94**) in 1960. This is formed as crystals on ozonization of *trans*-1,2-di-*tert*-butylethylene in pentane at -75° . **94** rearranges at -60° to form the *trans*-ozonide⁸⁹ (**95**), with liberation of nearly 40 kcal/mole. Thus the formation of **94** must liberate about 60 kcal/mole, since the total heat liberated during the conversion of the olefin into the ozonide is about 100 kcal/mole.⁹⁰ By reduction of **94** with isopropylmagnesium bromide to racemic di-*tert*-butylethylene glycol, it was shown that **94** still contains the original C—C bond of the olefin from which it was formed.⁸⁸



Whereas ozonides are stable to methanol even at room temperature, the primary ozonide (**94**) reacts with methanol to give methoxyhydroperoxide (**96**). This indicates the formation of a peroxidic zwitterion [Eq. (4)].

Greenwood^{91, 92} demonstrated the formation of primary ozonides in the reaction of some *trans*-olefins (*trans*-2-pentene, *trans*-3-hexene, and *trans*-2-butene, as well as 1-pentene and 1-butene). At -112° , the reaction with liquid ozone gave products that formed glycols on mild reduction with isopropylmagnesium bromide. On the other hand, primary ozonides have not been detected with certainty in the case of *cis*-olefins.^{88, 91} The reaction of *cis*-3-hexene,⁹³ *cis*-2-butene, *cis*-2-pentene, and ethylene⁹² with ozone at -112° in pentane led to extremely explosive substances, which could be primary ozonides. In the

⁸⁸ R. Criegee and G. Schröder, *Ber.* **93**, 689 (1960).

⁸⁹ G. Schröder, *Ber.* **95**, 733 (1962).

⁹⁰ E. Briner and E. Dallwigk, *Helv. Chim. Acta* **40**, 1978 (1957).

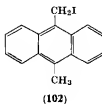
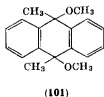
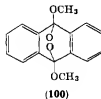
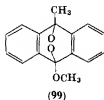
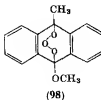
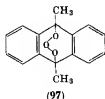
⁹¹ F. L. Greenwood, *J. Org. Chem.* **29**, 1321 (1964).

⁹² F. L. Greenwood, *J. Org. Chem.* **30**, 3108 (1965).

⁹³ F. L. Greenwood and B. J. Haske, *Tetrahedron Letters*, p. 631 (1965).

case of the *cis*-olefins, the stability of the primary ozonide should be influenced by steric factors and by solvent effects.^{91, 92}

De Bruyn⁹⁴ found that ozone adds to 9,10-dimethylantracene to form **97**. This product is obtained in almost quantitative yield when ozone is led into a solution of the anthracene derivative in acetone.



97 contains the seven-membered peroxide ring; the NMR spectrum contains only one methyl proton signal.⁹⁵ Similarly, 9-methoxy-10-methylantracene reacts with ozone to form the adduct (**98**).^{94, 95} NMR measurements show that **97** undergoes rearrangement at room temperature to give the endoperoxide (**99**), and **98** undergoes a similar rearrangement to form the endoperoxide (**100**).⁹⁵ Decomposition of **97** with CuCl_2 or CoCl_2 in methanol and catalytic hydrogenation in methanol lead to 9,10-dimethoxy-9,10-dimethyl-9,10-dihydroanthracene (**101**). **97** reacts with potassium iodide in glacial acetic acid to give 9-iodomethyl-10-methylantracene (**102**).^{94, 95}

⁹⁴ P. de Bruyn, *Bull. Soc. Chim. Belges* **69**, 328 (1960).

⁹⁵ R. E. Erickson, P. S. Bailey, and J. C. Davis, Jr., *Tetrahedron* **18**, 389 (1962).

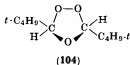
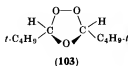
C. OZONIDES (1,2,4-TRIOXOLANS)

1. Preparation of Ozonides

Though the cleavage of olefins with ozone has been carried out for some 60 years on the basis of publications by Harries⁸² only a relatively small number of definite ozonides have been isolated and described. Criegee *et al.*⁹⁶ have published a table of definite ozonides. Reviews of the field have been published by Rieche,^{2,10} Long,⁹⁷ and Criegee,⁴ and the lectures of the "International Ozone Conference"⁹⁸ have also been published.

Monomeric ozonides are peroxidic acetals or ketals with the 1,2,4-trioxolan structure (6). They are mostly relatively stable distillable liquids or crystalline solids.⁹⁶ They exhibit no characteristic UV absorption,^{2,23,99} and the IR spectra⁹⁶ show medium to strong absorption between 1040 and 1060 cm^{-1} . No carbonyl bands are observed with pure ozonides.⁹⁶

Ozonides can occur as *cis-trans* isomers. On ozonization of *cis*-*tert*-butylethylene, Schröder⁸⁹ obtained a mixture of 70% of the *cis*-ozonide (103) and 30% of the *trans* isomer (104). Under the same reaction conditions, the *trans*-olefin gives only the *trans*-ozonide (104).



The assignment of the steric configurations of 103 and 104 is based on the different rates of the reduction with lithium aluminum hydride.⁸⁹ The *trans* isomer (104) is reduced more slowly because of steric factors. In both cases the reduction leads to a 78–80% yield of 2,2-dimethylpropanol.

In the ozonization of unsymmetrical olefins, cross reaction of zwitterions and carbonyl compounds can lead to six ozonides, i.e., three *cis-trans* pairs. This problem has recently been studied by a

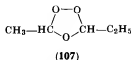
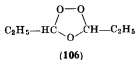
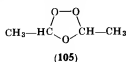
⁹⁶ R. Criegee, A. Kerckow, and H. Zinke, *Ber.* **88**, 1878 (1955).

⁹⁷ L. Long, *Chem. Rev.* **27**, 437 (1940).

⁹⁸ "Ozone Chemistry and Technology," *Advan. Chem. Ser.* **21** (1959).

⁹⁹ R. Criegee and G. Lohaus, *Ann.* **583**, 12 (1953).

number of authors.¹⁰⁰⁻¹⁰³ Whereas no stereoselectivity could be detected in the formation of the ozonides from methyl oleate, methyl elaidate,^{100, 101} and *cis*- and *trans*-hexene-3,⁹³ Lorenz and Parks¹⁰² found, in agreement with Schröder,⁸⁹ that the ratio of the *cis-trans* ozonides is highly dependent on the nature and steric configuration of the olefins. Loan *et al.*¹⁰³ used gas chromatography and NMR spectroscopy to study the ozonization of 2-pentene. At -70° pure 2-pentene forms the ozonides **105**, **106**, and **107** as *cis-trans* pairs in the



ratio 1:0.67:2.42. The proportion of **107** increases with increasing dilution of the ozonization mixture with pentane; this is thought to be due to a solvent cage effect.

According to Huisgen,⁸⁴ the formation of the ozonide by addition of the peroxidic zwitterion to a carbonyl group is a 1,3-dipolar addition. This explains the fact that, in the ozonization of open-chain olefins, ozonides are obtained as the principal products only when the carbonyl fragment has a sufficiently high dipolarophilic activity. This is so in the case of aldehydes, particularly formaldehyde; simple ketones, on the other hand, are less reactive. For this reason, aliphatic tetrasubstituted ethylenes do not normally form ozonides.⁸⁶

The ozonization of tetramethylethylene in the presence of formaldehyde leads to isobutene ozonide (**108**).¹⁰⁴ The zwitterion adds preferentially to formaldehyde, and not to acetone. The greater reactivity of the aldehyde group in comparison with the keto group is also seen in

¹⁰⁰ G. Riezebos, J. C. Grimmelikhuisen, and D. A. van Dorp, *Rec. Trav. Chim.* **82**, 1234 (1963).

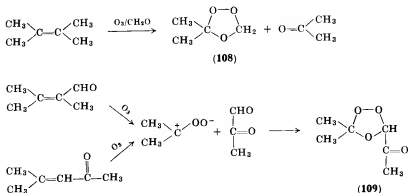
¹⁰¹ O. S. Privitt and E. C. Nickel, *J. Lipid Res.* **4**, 208 (1963); *J. Am. Oil Chemists' Soc.* **41**, 1 (1964); V. K. Kolsaker, *Acta Chem. Scand.* **19**, 223 (1965).

¹⁰² O. Lorenz and C. R. Parks, *J. Org. Chem.* **30**, 1976 (1965).

¹⁰³ L. D. Loan, R. W. Murray, and P. R. Story, *J. Am. Chem. Soc.* **87**, 737 (1965); F. L. Greenwood, *J. Am. Chem. Soc.* **88**, 3146 (1966).

¹⁰⁴ R. Criegee, G. Blust, and H. Zinke, *Ber.* **87**, 766 (1954).

the ozonization of trimethylacrolein, which gives the same ozonide (**109**) as is obtained from mesityl oxide.¹⁰⁵ The addition of a zwitterion to a ketone has only recently been achieved. Murray *et al.*¹⁰⁶ report that 2-pentene gives two ket-ald-ozonides on ozonization in acetone. The structures of these ozonides were established by NMR measurements.



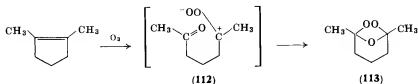
However, aliphatic ketozonides can be obtained in good yields if the carbonyl group of the ketone is activated by electron-attracting substituents. Thus 1,4-dibromo-2,3-dimethylbutene-2 and methyl trimethylacrylate give the ozonides **110** and **111**.¹⁰⁵



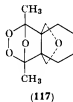
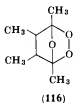
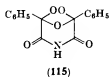
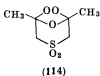
Ketozonides can also be formed when the keto group and the zwitterion are present in the same molecule and when the distance between them is suitable for ring closure. These conditions are satisfied in the ozonization of 1,2-disubstituted cycloalkenes containing five-membered rings, and even in those containing four-membered rings. Thus 1,2-dimethylcyclopentene forms the ketozonide (**113**) via the zwitterion (**112**).²⁴

¹⁰⁵ R. Criegee, S. S. Bath, and B. von Bornhaupt, *Ber.* **93**, 2891 (1960).

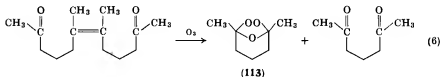
¹⁰⁶ R. W. Murray, P. R. Story, and L. D. Loan, *J. Am. Chem. Soc.* **87**, 3025 (1965).



113 has also been synthesized "without ozone"^{12, 23} by reaction of the corresponding diketone with hydrogen peroxide.²⁴ **114** is obtained from the cyclic sulfone of 2,3-dimethyl-1,3-butadiene,⁹⁹ and **115** is obtained from substituted maleimides.^{96, 107} Tetramethylcyclobutene reacts with ozone to form the ozonide (**116**),^{108, 109} and the crystalline ozonide (**117**) is obtained from the corresponding cyclobutene derivative.¹¹⁰



Open-chain olefins with keto groups in the molecule can also undergo intramolecular reaction to form ketozonides, e.g., **113** [Eq. (6)].¹¹¹



¹⁰⁷ J. E. Richmond and K. J. Altman, *J. Am. Chem. Soc.* **74**, 4368 (1952).

¹⁰⁸ R. Criegee, *Angew. Chem.* **74**, 704 (1962).

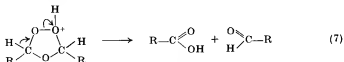
¹⁰⁹ R. Criegee, Lecture at the Institut für Organische Chemie der Deutschen Akademie der Wissenschaften, Berlin-Aldershof, 1963.

¹¹⁰ R. Askani, *Ber.* **98**, 2322 (1965).

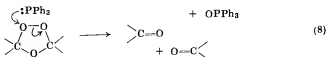
¹¹¹ G. Lohaus, *Ber.* **87**, 1708 (1954).

2. *Reactions of the Ozonides*

The determination of the active oxygen in ozonides with sodium iodide in glacial acetic acid gives reliable values only in the case of ketozonides. The reaction products are ketones.⁹⁶ Iodometric peroxide determination in the case of aldazonides gives less than 60% of the theoretical value;¹¹² carboxylic acids are formed as well as aldehydes. The reduction with iodide ions probably suffers competition from the reaction shown in Eq. (7).



The reduction of ozonides with triphenylphosphine,¹¹³ on the other hand, proceeds quantitatively with both ketozonides and aldazonides. Lorenz^{102, 112} used this reaction as the basis of a method for the determination of ozonides. The reaction mechanism is probably as shown in Eq. (8).¹⁰²



Catalytic hydrogenation¹¹⁴⁻¹¹⁶ also leads to carbonyl compounds, acids being formed in a side reaction.¹¹⁶ Reduction of the ozonides with lithium aluminum hydride¹¹⁷⁻¹¹⁹ and with sodium borohydride¹¹⁹ yields alcohols.

In a reversal of the formation of ozonides "without ozone," Rieche *et al.*²³ obtained dihydroxydialkyl peroxides (2) as the first isolable products by acid hydrolysis of ozonides.

Witkop and Patrick¹²⁰ suggested that the hydrolysis of 2-phenylskatole ozonide (118) to the ketone (120) may involve an acid-base

¹¹² O. Lorenz, *Anal. Chem.* **37**, 101 (1965).

¹¹³ L. Horner and W. Jurgeleit, *Ann.* **591**, 138 (1955).

¹¹⁴ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **74**, 3855 (1952).

¹¹⁵ P. S. Bailey, *Ber.* **87**, 993 (1954).

¹¹⁶ F. G. Fischer, H. Düll, and L. Ertel, *Ber.* **65**, 1467 (1932).

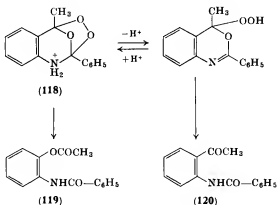
¹¹⁷ F. L. Greenwood, *J. Org. Chem.* **20**, 803 (1955).

¹¹⁸ H. Lettré and D. Hotz, *Angew. Chem.* **69**, 267 (1957).

¹¹⁹ J. A. Sousa and A. L. Bluhm, *J. Org. Chem.* **25**, 108 (1960).

¹²⁰ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **74**, 3861 (1952).

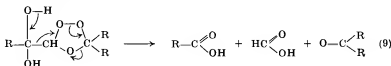
catalyzed ring-chain tautomerism. The cleavage of **118** (as the sulfate) in acetic anhydride leads to rearrangement and formation of **119**.¹²⁰



The oxidative cleavage of ozonides leads to carboxylic acids. This cleavage is carried out by treatment of the crude ozonization product with alkaline silver oxide, potassium permanganate, or hydrogen peroxide solution,¹²¹ or with peracetic acid.¹²²

The ozonization of some α,β -unsaturated acids, aldehydes, and ketones proceeds "abnormally" in the presence of water, the C—C bond adjacent to the carbonyl group being cleaved as well as the C=C double bond.⁸ Barton and Seoane¹²³ formulated this reaction as formation of the ozonide, followed by decomposition by a concerted mechanism, in which water plays an important part; see also Refs. 124 and 125.

In ozonides with adjacent carbonyl groups, the fragmentation is introduced by hydration of the carbonyl group [Eq. (9)].^{8,124}



¹²¹ F. Asinger, *Ber.* **75**, 656 (1942).

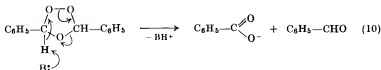
¹²² H. Wilms, *Ann.* **567**, 96 (1950).

¹²³ D. H. R. Barton and E. Seoane, *J. Chem. Soc.* p. 4150 (1956).

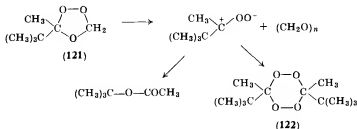
¹²⁴ J. Knights and E. S. Waight, *J. Chem. Soc.* p. 2830 (1955).

¹²⁵ W. G. Dauben, H. G. Wight, and G. A. Boswell, *J. Org. Chem.* **23**, 1787 (1958).

Aldozonides are more sensitive towards alkalis than towards acids. The base evidently attacks the α -hydrogen atom of the ozonide. An example of this is probably the decomposition of stilbene ozonide to give benzoic acid and benzaldehyde [Eq. (10)].¹²⁶



Relatively little study has been carried out on the thermal decomposition of ozonides. This is a complicated reaction, which generally leads to a mixture of cleavage products.¹²⁷ The decomposition of 2-butene ozonide^{23, 34} and of 2,3,3-trimethylbut-1-ene ozonide⁹⁶ (**121**) also yields dimeric alkylidene peroxides, e.g., **122**. These are thought to be formed via the peroxidic zwitterion.



Carboxylic acid derivatives were obtained in the decomposition of **123**¹²⁸ and **124**.¹²⁹

The fact that the decomposition of ozonides is catalyzed by finely divided metals (silver, platinum, palladium) and metal salts such as ferrous sulfate suggests a free-radical mechanism.²³ 2-Butene ozonide is broken down with dilute ferrous sulfate solution into acetic acid and acetaldehyde.²³

D. 1,2,4,5-TETROXANS AND OTHER CYCLIC PEROXIDES

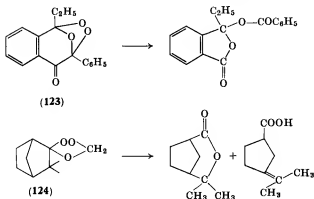
On ozonization in solvents that do not contain hydroxyl groups, tetrasubstituted olefins with aliphatic or aromatic residues give 1,2,4,5

¹²⁶ R. Criegee, private communication, 1965.

¹²⁷ E. Briner, *Helv. Chim. Acta* **22**, 591 (1939).

¹²⁸ R. Criegee, P. de Bruyn, and G. Lohaus, *Ann.* **583**, 19 (1953).

¹²⁹ P. S. Bailey, *Ber.* **88**, 795 (1957).



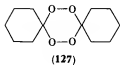
tetroxans ("dimeric ketone peroxides") as the principal products, in accordance with Eq. (3). Ozonide formation does not occur, owing to the weak 1,3-dipolarophilic activity of the ketone formed.

Thus the ozonization of tetramethylethylene leads to dimeric acetone peroxide (**125**)⁸⁶ (as well as trimeric acetone peroxide), that of tetraphenylethylene¹³⁰ and 1,1-diphenylethylene⁶² leads to

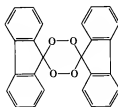


(125): $\text{R} = \text{CH}_3$

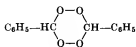
(126): $\text{R} = \text{C}_6\text{H}_5$



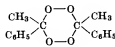
(127)



(128)



(129)



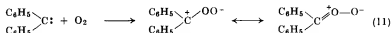
(130)

¹³⁰ C. S. Marvel and V. Nichols, *J. Org. Chem.* **6**, 296 (1941).

dimeric benzophenone peroxide (126), dicyclohexylidene gives dimeric cyclohexanone peroxide (127),⁸⁶ and bisbiphenylen-ethylene gives dimeric fluorenone peroxide (128).⁸⁶

Even where an aldehyde is formed as a carbonyl fragment in the ozonolysis of an olefin, 1,2,4,5-tetroxans are often formed in a side reaction, depending on the solvent,¹³¹ the concentration, and the ozonization temperature. Thus dimeric acetone peroxide is obtained from isobutylene,¹³² dimeric benzaldehyde peroxide (129) from styrene¹³² and stilbene,^{96, 132} and dimeric acetophenone peroxide (130) from α -methylstyrene.¹³²

Photolysis of diphenyldiazomethane at -70° in the presence of oxygen leads to an 8% yield of dimeric benzophenone peroxide (126).¹³³ This peroxide is again formed via the peroxidic zwitterion (carbonyl oxide) [in accordance with Eq. (3)], which results from the autoxidation of diphenylcarbene [Eq. (11)]. The principal products of the ozonization of cyclic olefins in which the double bond is shared by two rings are 1,2,4,5-tetroxans. $\Delta^9, 10$ -Octalin gives the dimeric



peroxide of cyclodecandione-1,6 (131),⁸⁵ the reaction involving the intermediate 132. $\Delta^8, 9$ -Hexahydroindene¹³⁴ reacts with ozone in a similar manner.

In the ozonization of rubber, Harries¹³⁵ obtained a peroxide which was shown by Pummerer *et al.*¹³⁶ to be the dimeric peroxide of levulinic acid (133), and which can be synthesized from the acid with concentrated hydrogen peroxide.¹³⁷ 133 is partly converted into succinic acid on treatment with acid.

According to Bailey *et al.*,⁴⁶ the ozonization of naphthalene in methanol proceeds with participation of the solvent, and yields the crystalline cyclic peroxide (135), which has a six-membered ring structure. This peroxide results from the intramolecular stabilization

¹³¹ R. Criegee, in "Peroxide Reaction Mechanisms" (J. O. Edwards, Ed.), p. 38. Wiley (Interscience), New York, 1962.

¹³² N. A. Milas, P. Davis, and J. T. Nolan, Jr., *J. Am. Chem. Soc.* **77**, 2536 (1955).

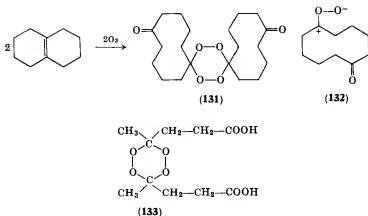
¹³³ P. D. Bartlett and T. G. Traylor, *J. Am. Chem. Soc.* **84**, 3408 (1962).

¹³⁴ R. Criegee and H. Zobel, *Ber.* **84**, 215 (1951).

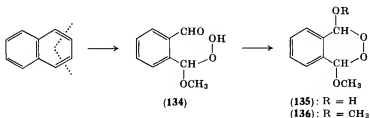
¹³⁵ C. Harries, *Ber.* **38**, 1195 (1905).

¹³⁶ R. Pummerer, G. Ebermayer, and K. Gerlach, *Ber.* **64**, 804 (1931).

¹³⁷ F. Fichter and S. Lurie, *Helv. Chim. Acta* **16**, 885 (1933).



[in accordance with Eq. (5)] of the methoxyhydroperoxide (134), which is formed by addition of methanol to the zwitterion.¹³⁸ Concerning the fate of the C_2 fragment, see Johnson and Bailey.¹³⁹ The 3-methoxy-6-hydroxy-4,5-benzodioxene (135), which is obtained in 91% yield, also arises (though in a lower yield) by ozonization of 2,3-dimethylnaphthalene or β -naphthol. The ozonization of 2-methoxy- and 2-ethoxynaphthalenes in methanol leads to the dimethoxyperoxide (136). The ethoxy analog of 136 is obtained by ozonization of 2-ethoxynaphthalene in ethanol.⁸⁷



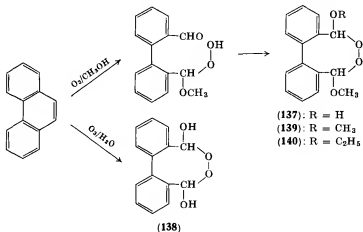
On treatment with acids or bases, both the monomethoxy and the dimethoxy six-membered ring peroxide are converted into the methyl ester of *o*-phthalaldehydic acid or into *o*-phthalaldehydic acid, depending on the reaction conditions. Oxidation with hydrogen peroxide yields *o*-phthalic acid.⁸⁷ The hydrogenation of 135 in the presence of a Lindlar catalyst leads to *o*-phthalaldialdehyde (yield =

¹³⁸ A. Rieche and M. Schulz, *Ber.* **97**, 190 (1964).

¹³⁹ C. D. Johnson and P. S. Bailey, *J. Org. Chem.* **29**, 703 (1964).

55%) which is thus readily obtainable from naphthalene in this way.¹³⁸

The ozonolysis of phenanthrene in methanol leads to the eight-membered ring peroxide (**137**).^{140, 141} When phenanthrene is ozonized in the presence of water, it gives the cyclic dihydroxyperoxide (**138**), which is also formed from diphenylaldehyde and hydrogen peroxide.¹⁴²



The hydroxyl group in **137** can be readily replaced by a methoxyl group to give **139** or by an ethoxyl group to give **140**.¹⁴¹

Reduction of the eight-membered ring peroxide (**137**) with potassium iodide in glacial acetic acid leads to an 84% yield of 2,2'-diphenyl-dialdehyde.¹⁴¹ The base-catalyzed decomposition of **137** gives 2,2'-diphenaldehydic acid in 84% yield. Diphenic acid (84%) is obtained when **139** is heated with a mixture of 30% hydrogen peroxide and 10% sodium hydroxide solution.¹⁴¹

A seven-membered ring peroxide, to which structure **141** has been assigned, was obtained by Warnell and Shriner¹⁴³ on ozonization of indene in ethanol. From the reported melting range of the

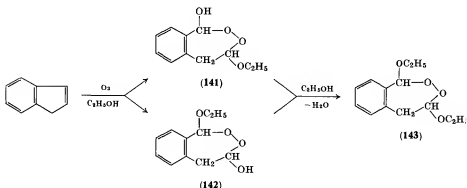
¹⁴⁰ J. P. Wibaut and J. J. de Boer, *Koninkl. Ned. Akad. Wetenschap. Proc. Ser. B* **59**, 421 (1956).

¹⁴¹ P. S. Bailey, *J. Am. Chem. Soc.* **78**, 3811 (1956); P. S. Bailey and S. B. Mainthai, *J. Org. Chem.* **23**, 1089 (1958).

¹⁴² M. G. Sturrock, E. L. Cline, and K. R. Robinson, *J. Org. Chem.* **28**, 2340 (1963).

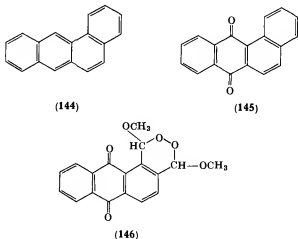
¹⁴³ J. L. Warnell and R. L. Shriner, *J. Am. Chem. Soc.* **79**, 3165 (1953).

semicrystalline product, it may be assumed that this is a mixture of two isomeric peroxides, **141** and **142**. Reaction of the product with ethanol in the presence of a little acid yields the diethoxy compound (**143**), which is well-defined and which crystallizes well.



The hydroxy compounds **141** and **142**, as well as **143**, are decomposed by alkali to give *o*-carboxyphenylacetaldehyde. Oxidation with basic hydrogen peroxide leads to homophthalic acid; reduction with zinc dust and a trace of acetic acid gives homophthalaldehyde, and reduction with lithium aluminum hydride gives homophthalyl alcohol.

The ozonization of benzo-[*a*]-anthracene (**144**) and of benzo-[*a*]-anthracene-7,11-dione (**145**) in methanol leads to the cyclic dimethoxy-



peroxide (**146**).¹⁴⁴ Oxidation with alkaline hydrogen peroxide converts **146** into the corresponding dicarboxylic acid, and reduction with potassium iodide in acetic acid gives 1,2-anthraquinonedialdehyde.

The preparative use of the ozonization of cyclic olefins in methanol, which leads to eight-membered ring peroxides, has been discussed for the steroid series by Lettré and Hotz.¹⁴⁵

IV. Syntheses of Cyclic Peroxides with Oxygen

A. CYCLIC PEROXIDES BY AUTOXIDATION

Autoxidation¹⁴⁶ of suitable olefins, particularly 1,3-dienes, leads to cyclic peroxides (though mostly in low yields) as well as polymeric peroxides. These autoxidations occur when the olefins are aerated with oxygen, and does not usually require exposure to light or the use of sensitizers. Only a few papers have been published in this field, and these are mostly due to Hock *et al.*¹⁴⁷⁻¹⁵³

Following the autoxidation of cyclohexa-1,3-diene and cyclopentadiene at 15 to 20°, Hock and Depke¹⁴⁷ isolated small yields of the cyclic peroxides **147** and **148**, respectively. **147** can be obtained in better yields by photosensitized oxidation of cyclohexa-1,3-diene (see Section IV, B) and by the action of hydrogen peroxide and sodium hypochlorite on cyclohexa-1,3-diene¹⁵⁴. In the last reaction, oxygen

¹⁴⁴ E. J. Moriconi, W. F. O'Connor, and F. T. Wallenberger, *J. Am. Chem. Soc.* **81**, 6466 (1959).

¹⁴⁵ H. Lettré and D. Hotz, *Ann.* **620**, 63 (1959).

¹⁴⁶ A. Rieche, E. Schmitz, and M. Schulz, *Z. Chem.* **3**, 443 (1963) have suggested that reactions in which peroxides are formed by the action of oxygen should be called "peroxygenations." Where the organic compounds take up the oxygen in nonperoxidic bonds, the reaction should be known as "oxygenation." These two types of reactions would thus be distinguished from "dehydrogenations." The conventional term "autoxidation" will be used in this chapter.

¹⁴⁷ H. Hock and F. Depke, *Ber.* **84**, 349 (1951).

¹⁴⁸ H. Hock and M. Siebert, *Ber.* **87**, 546 (1954); see also F. R. Mayo and A. A. Miller, *J. Am. Chem. Soc.* **80**, 2480 (1958).

¹⁴⁹ H. Hock and F. Depke, *Ber.* **84**, 122 (1951); see also J. A. Russel, *J. Am. Chem. Soc.* **78**, 1035 (1956).

¹⁵⁰ H. Hock and H. Kropf, *Angew. Chem.* **69**, 313 (1957) (review).

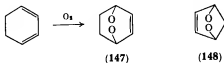
¹⁵¹ H. Hock and F. Depke, *Ber.* **83**, 317 (1950).

¹⁵² H. Hock, S. Lang, and G. Knaul, *Ber.* **83**, 227 (1950).

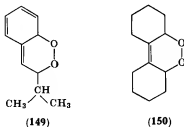
¹⁵³ H. Hock and M. Siebert, *Ber.* **87**, 554, (1954).

¹⁵⁴ C. S. Foote and S. Wexler, *J. Am. Chem. Soc.* **86**, 3879 (1964).

acts in an excited singlet state. The mechanism of this reaction is discussed out by Foote *et al.*¹⁵⁵ and Corey and Taylor.¹⁵⁶



Vinyl-substituted aromatic compounds such as α -methylstyrene,¹⁴⁸ β -isopropylstyrene,¹⁴⁸ 1-phenylcyclohexene,¹⁵³ indene,¹⁴⁹ and 1,2-dihydronaphthalene^{151,152} give cyclic peroxides on autoxidation. For example, β -isopropylstyrene gives the 1,2-dioxene derivative (149) together with polymeric peroxide. After the *tert*-alkyl hydroperoxide formed by attack of oxygen on the isopropyl group had been reduced with sodium sulfite, 149 could be isolated in 26.4% yield by means of an alumina column.



The autoxidation of bicyclohexenyl leads to a mixture of cyclic peroxide (150), hydroperoxide, and polymeric peroxide.¹⁵³

Cyclic peroxides are also formed in the autoxidation of polyolefinic acids¹⁵⁷ and squalene.^{158,159}

According to Wittig and Lupin,¹⁶⁰ the cyclic peroxide (151) is formed when a suspension of 1,4-dipotassium 1,1,4,4-tetraphenylbutane in ether is treated with dry oxygen. The peroxide (152) is formed, though in small quantities, during the autoxidation of di-(*p*-anisyl)ethylene in benzaldehyde, by combination of two molecules of

¹⁵⁵ C. S. Foote and S. Wexler, *J. Am. Chem. Soc.* **86**, 3880 (1964); C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Letters*, p. 4111 (1965).

¹⁵⁶ E. J. Corey and C. Taylor, *J. Am. Chem. Soc.* **86**, 3881 (1964).

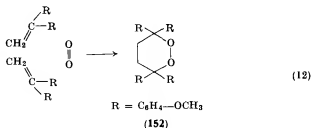
¹⁵⁷ R. N. Faulkner, *J. Appl. Chem.* **8**, 448 (1958).

¹⁵⁸ J. L. Bolland and P. ten Have, *Trans. Faraday Soc.* **45**, 93 (1949).

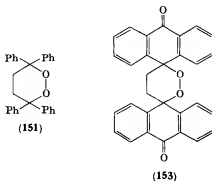
¹⁵⁹ J. L. Bolland and H. Hughes, *J. Chem. Soc.* p. 492 (1949).

¹⁶⁰ G. Wittig and von Lupin, *Ber.* **61**, 1627 (1928).

di-(*p*-anisyl)ethylene with 1 mole of oxygen [in accordance with Eq. (12)].¹⁶¹ The autoxidation of methyleneanthrone in light also proceeds with formation of a C—C bond to give **153**.¹⁶² These reactions leading to the formation of **151**, **152**, and **153** are special cases of autoxidation,



and no other analogous reactions are known at present.



McKay *et al.*¹⁶³ reported a 1,4 addition of oxygen to the enamine derivatives (**154**, **155**, and **156**). These compounds react with oxygen in chloroform within an hour at room temperature to give 1,2,4-dioxazine derivatives (**157**, **158**, and **159**). In the presence of 0.1 % cobalt naphthenate, 1 meq of oxygen is taken up in less than 5 minutes.

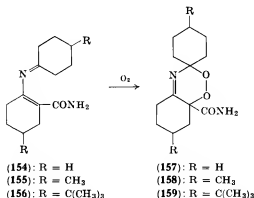
Ikeda *et al.*¹⁶⁴ obtained good yields of spiro peroxides of type **162** on autoxidation of 1,3-dioxolans with vinyl substituents in position 2 (**160**). The reaction proceeds via allyl hydroperoxide intermediates (**161**).

¹⁶¹ G. Wittig and W. Gauss, *Ber.* **80**, 363 (1947).

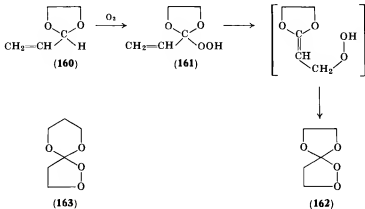
¹⁶² A. Mustafa and H. M. Islam, *J. Chem. Soc. Suppl.*, p. 81 (1949).

¹⁶³ A. F. McKay, I. M. Billy, and E. J. Tarlton, *J. Org. Chem.* **29**, 291 (1964).

¹⁶⁴ C. K. Ikeda, R. A. Braun, and B. E. Sorenson, *J. Org. Chem.* **29**, 286 (1964).



A similar course is followed by the autoxidation of 2-vinyl-1,3-dioxans, which leads to cyclic peroxides of type **163**.



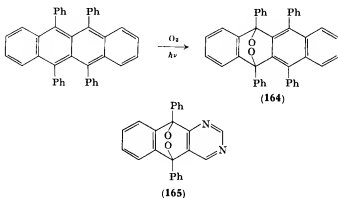
B. CYCLIC PEROXIDES BY PHOTOOXIDATION

The autoxidation of 1,3-dienes is generally of minor importance for the synthesis of cyclic peroxides, the principal route to which is the photooxidation of 1,3-dienes. For this process, a sensitizer must be added in the case of low molecular weight 1,3-dienes and the 1,3-dienes of the terpene and steroid series. No sensitizer is required in the photooxidation of condensed aromatic hydrocarbons. These reactions may be regarded as diene syntheses with oxygen as the dienophile.¹⁶⁵ A

¹⁶⁵ K. Alder and M. Schumacher, *Fortschr. Chem. Org. Naturstoffe* **10**, 47 (1958).

recent survey of the entire field was published by Gollnick and Schenck.¹⁰

The formation of acene peroxides was studied by Dufraisse *et al.*^{9, 166} A classical example of this reaction is the formation of rubrene peroxide (**164**) from rubrene and oxygen.¹⁶⁷



Similar endoperoxides¹⁶⁸ of anthracene¹⁶⁹ to hexacene¹⁷⁰ and of many meso-substituted aromatic hydrocarbons are known.^{9, 10, 166} The nature of the meso substituent has a strong effect on peroxide formation. Endoperoxides are not formed by compounds with cyano, carboxy, or carboalkoxy substituents in the meso position.¹⁷¹ Endoperoxides, e.g., **165**, have also been obtained from acenes containing a condensed heterocycle.¹⁷²⁻¹⁷⁴

The course of the photooxidation of acenes depends on the solvent. Endoperoxides are formed above all in carbon disulfide, as well as in

¹⁶⁶ C. Dufraisse, *Bull. Soc. Chim. France* [5] **5**, 1073 (1938).

¹⁶⁷ C. Moureu, C. Dufraisse, and P. M. Dean, *Compt. Rend.* **182**, 1440 and 1584 (1926).

¹⁶⁸ These cyclic peroxides are also known as photooxides, transannular peroxides, 1,4-epiperoxides, and epidioxides.

¹⁶⁹ C. Dufraisse and M. Gerard, *Compt. Rend.* **201**, 428 (1935).

¹⁷⁰ E. Clar, *Ber.* **72**, 1817 (1939).

¹⁷¹ C. Dufraisse and R. Priou, *Compt. Rend.* **212**, 906 (1941).

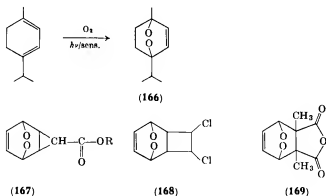
¹⁷² A. Étienne, *Ann. Chim. (Paris)* [12] **1**, 5 (1946).

¹⁷³ A. Étienne and R. Roberts, *Compt. Rend.* **223**, 331 (1946).

¹⁷⁴ M. Legrand, *Compt. Rend.* **237**, 822 (1953).

chloroform; in benzene and ether, on the other hand, the hydrocarbons dimerize.¹⁷⁵⁻¹⁷⁷

In true "photosensitized autoxidation," the addition of a sensitizer, such as chlorophyll, eosin, or rose bengal, is essential. This method was pioneered by Windaus and Brunken¹⁷⁸ in the steroid series (ergosterol peroxide) and by Schenck and Ziegler¹⁷⁹ in the terpene series (ascaridole). Schenck *et al.*^{10, 180, 181} generalized the applicability of photosensitized autoxidation.



Schenck and Ziegler¹⁷⁹ obtained the naturally occurring endoperoxide ascaridole (**166**) by irradiation of an alcoholic solution of α -terpinene in the presence of eosin. Endoperoxides similar to **166** are formed in the photosensitized autoxidation of cyclopentadiene,¹⁸² cyclohexa-1,3-diene,^{179, 182} cyclohepta-1,3-diene,¹⁸³ and their phenyl-

¹⁷⁵ R. Livingston and V. S. Rao, *J. Phys. Chem.* **63**, 794 (1959).

¹⁷⁶ R. Livingston, in "Photochemistry in the Liquid and Solid States" (L. J. Heidt, R. S. Livingston, E. Rabinowitch, and F. Daniels, eds.), p. 76. Wiley, New York, 1960.

¹⁷⁷ R. Livingston, in "Autoxidation and Antioxidants" (O. Lundberg, ed.), Vol. 1, p. 249. Wiley (Interscience), New York, 1961.

¹⁷⁸ A. Windaus and J. Brunken, *Ann.* **460**, 225 (1928).

¹⁷⁹ G. O. Schenck and K. Ziegler, *Naturwissenschaften* **32**, 157 (1944).

¹⁸⁰ A. Schönberg, "Präparative organische Photochemie," p. 52. Springer, Berlin, 1958.

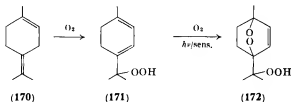
¹⁸¹ G. O. Schenck, in "Fiat Reviews" (K. Ziegler, ed.), German ed., Vol. 37, Pt. 2, p. 167. Verlag Chemie, Weinheim, 1953.

¹⁸² G. O. Schenck and D. E. Dunlap, *Angew. Chem.* **68**, 248 (1956).

¹⁸³ A. C. Cope, T. A. Liss, and S. N. Wood, *J. Am. Chem. Soc.* **79**, 6287 (1957).

substituted derivatives,¹⁸⁴⁻¹⁸⁶ as well as triphenyltin-substituted cyclopentadienes.¹⁸⁷ Other interesting cyclic peroxides include **167**,^{188, 189} **168**,¹⁹⁰ and **169**. **169** is an intermediate in a synthesis of cantharidin.¹⁹¹

The photosensitized autoxidation of terpinolene (**170**) leads initially to an allyl shift of the double bond with formation of the hydroperoxide intermediate (**171**), which reacts further to give the cyclic peroxide (**172**).^{192, 193}



Ergosterol peroxide,¹⁷⁸ which was prepared as early as 1928, was shown by Skau and Bergmann¹⁹⁴ and Bergmann and Hirschmann¹⁹⁵ to have the endoperoxide structure (**173**) (α structure). **174**, which is an intermediate in the synthesis of compounds related to cortisone,¹⁹⁶ contains the peroxide bridge in ring C (α structure). The cyclic peroxide (**175**), which contains the peroxide group in ring A (β structure), was obtained by UV irradiation of $\Delta^{2,4}$ -cholestadiene in absolute alcohol in the presence of eosin.

According to Bergmann and Hirschmann,¹⁹⁵ only homoannular dienes of the steroids are expected to give endoperoxides. The for-

¹⁸⁴ J. Rigaudy and P. Courtot, *Tetrahedron Letters*, p. 95 (1961).

¹⁸⁵ G. O. Schenck, W. Müller, and A. Pfennig, *Naturwissenschaften* **41**, 374 (1954).

¹⁸⁶ J. R. Evanega, W. Bergmann, and G. English, Jr., *J. Org. Chem.* **27**, 13 (1962).

¹⁸⁷ G. O. Schenck, E. Koerner von Gustorf, and H. Köller, *Angew. Chem.* **73**, 707 (1961).

¹⁸⁸ G. O. Schenck and H. Ziegler, *Naturwissenschaften* **38**, 356 (1951).

¹⁸⁹ G. O. Schenck, *Z. Elektrochem.* **56**, 860 (1952).

¹⁹⁰ G. Grebe, Dissertation, Universität Göttingen, 1952.

¹⁹¹ G. O. Schenck and R. Wirtz, *Naturwissenschaften*, **40**, 581 (1953).

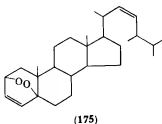
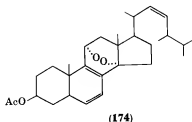
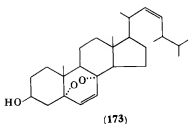
¹⁹² G. O. Schenck, *Angew. Chem.* **64**, 12 (1952).

¹⁹³ G. O. Schenck, *Angew. Chem.* **69**, 579 (1957).

¹⁹⁴ E. L. Skau and W. Bergmann, *J. Org. Chem.* **3**, 166 (1938).

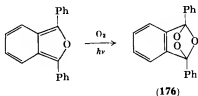
¹⁹⁵ W. Bergmann and F. Hirschmann, *J. Org. Chem.* **4**, 40 (1939).

¹⁹⁶ G. D. Laubach, E. C. Schreiber, E. J. Agnello, E. N. Lightfoot, and K. J. Brunings, *J. Am. Chem. Soc.* **75**, 1514 (1953).



mation of the peroxide bridge in the α or β position appears to be influenced by the C-10 methyl group.

The action of oxygen on furan and furan derivatives in light leads to 1,4 addition with formation of ozonides.¹⁹⁷ However, the only case in which the ozonide has been isolated is that of 1,4-diphenylisobenzofuran; this gives the crystalline ozonide (176), which explodes at 18°.¹⁹⁸ In most cases only the decomposition products of the ozonides (carbonyl compounds, acids, and their derivatives) are isolated.



Endoperoxides are also thought to occur as intermediates in the oxidation of thiophen¹⁹⁹ and pyrrole derivatives.²⁰⁰

Theilacker and Schmidt²⁰⁰ obtained the stable endoperoxide (177), which contains nitrogen, by the reaction of 1,2,3-triphenylisindole

¹⁹⁷ G. O. Schenck, *Ann.* **584**, 156 (1953).

¹⁹⁸ C. Dufraisse and S. Ecury, *Compt. Rend.* **223**, 735 (1946).

¹⁹⁹ A. Mustafa, *J. Chem. Soc.* p. 256 (1949).

²⁰⁰ W. Theilacker and W. Schmidt, *Ann.* **605**, 43 (1957).

with oxygen in carbon disulfide; no sensitizer was required in this case. Whereas **176** is explosive, **177** can be handled without danger.

According to White and Harding,²⁰¹ the cyclic peroxide reported in the photochemical oxidation of lophine (2,3,5-triphenylimidazole)^{202, 203} is the hydroperoxide (**178**).



For discussions on the mechanism of photosensitized reactions, the reader is referred to the publications by Schenck^{10, 193} and Hammond *et al.*²⁰⁴⁻²⁰⁶ See also Foote and Wexler¹⁵⁴ and Saltiel.²⁰⁷

C. REACTIONS OF THE CYCLIC PEROXIDES OBTAINED BY PHOTOOXIDATION

1. Reduction

Ascaridol (**166**) forms the saturated *cis*-1,4-diol (**179**) on catalytic hydrogenation in the presence of colloidal palladium²⁰⁸ or freshly prepared Raney nickel.²⁰⁹ When palladium²¹⁰ saturated with hydrogen or platinum dioxide²¹¹ is used, dihydroascaridole (**181**) is formed, with retention of the peroxide bridge. K-Na alloys in ether, zinc and zinc chloride in methanol,²⁰⁹ and the hydrogenation in

²⁰¹ E. H. White and M. J. C. Harding, *J. Am. Chem. Soc.* **86**, 5686 (1964).

²⁰² C. Dufraisse, A. Étienne, and J. Martel, *Compt. Rend.* **244**, 920 and 3106 (1957).

²⁰³ C. Dufraisse and J. Martel, *Compt. Rend.* **245**, 456 (1957).

²⁰⁴ R. S. Liu, N. J. Turro, Jr., and G. S. Hammond, *J. Am. Chem. Soc.* **87**, 3406 (1965).

²⁰⁵ G. S. Hammond and R. S. Cole, *J. Am. Chem. Soc.* **87**, 3256 (1965).

²⁰⁶ G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Am. Chem. Soc.* **86**, 3197 (1964).

²⁰⁷ J. Saltiel, *Survey of Progr. Chem.* **2**, 313 (1964).

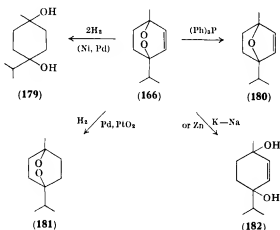
²⁰⁸ O. Waller, *Ann.* **392**, 49 (1912).

²⁰⁹ G. O. Schenck, K. G. Kinkel, and H.-J. Mertens, *Ann.* **584**, 125 (1953).

²¹⁰ H. Paget, *J. Chem. Soc.* p. 829 (1938).

²¹¹ C. G. Moore, *J. Chem. Soc.* p. 234 (1951).

presence of the Lindlar catalyst²¹² lead to reduction of only the peroxide group, the double bond remaining intact to give **182**. Reduction with triphenylphosphine leads to the formation of an endo-oxide bridge (**180**).¹¹³



This reaction scheme can also be applied to other endoperoxides such as norascaridole,²¹³ endoperoxides of α -phellandrene^{214, 215} and α -pyronene,²¹⁶ and ergosterol peroxide.²¹⁷

Other reducing agents, which lead to unsaturated glycols of type **182**, include thiourea,¹⁸² aluminum amalgam,²¹⁴ and lithium aluminum hydride.^{192, 218} The reaction of dihydroascaridole (**181**) with ferrous sulfate or titanous chloride yields propane and 4-hydroxy-4-methylcyclohexanone while ascaridol gives 3,6-endo-4-isopropyl-6-methylcyclohexane-1,2-diol and 4-hydroxy-3-isopropylcyclohexa-

²¹² G. D. Laubach, E. C. Schreiber, E. J. Agnello, and K. J. Brunings, *J. Am. Chem. Soc.* **78**, 4756 (1956).

²¹³ D. E. Dunlap, Dissertation, Universität Göttingen, 1957.

²¹⁴ G. O. Schenck and K. Ziegler, *Festschr. Arthur Stoll, 1957* Birkenhäuser Verlag, Basel, p. 620 (1957).

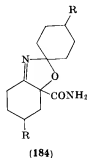
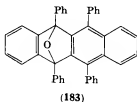
²¹⁵ A. Blumann, E. W. Della, C. A. Henrick, J. Hodgkin, and P. R. Jefferies, *Australian J. Chem.* **15**, 290 (1962).

²¹⁶ G. O. Schenck, *Z. Elektrochem.* **55**, 505 (1951).

²¹⁷ R. B. Clayton, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.* p. 2015 (1953).

²¹⁸ G. O. Schenck, H. Eggert, and W. Denk, *Ann.* **584**, 177 (1953).

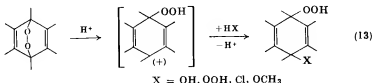
none.^{210, 219-221} Reduction of rubrene peroxide (**164**)^{222, 223} and of the 1,2,4-dioxazine derivatives (**157-159**)¹⁶³ with zinc leads to the cyclic ethers **183** and **184**.



Mustafa²²⁴ reduced 9,10-diphenylanthracene peroxide to the corresponding 9,10-dihydroxy derivative by boiling for 2 hours with phenylmagnesium bromide solution.

2. Action of Acids and Bases

The C—O bond in some acene peroxides is heterolyzed by the action of mineral acids to form hydroperoxides, in accordance with Eq. (13).



Water, hydrogen peroxide, methanol, or chloride add to the intermediate cation.²²⁵ The endoperoxide of 9-methoxy-10-phenylanthracene (**185**) gives the 9-oxo-10-hydroperoxyanthracene (**186**).²²⁶

²¹⁹ D. Brown, B. T. Davis, and T. G. Halsall, *J. Chem. Soc.* p. 1095 (1963).

²²⁰ D. Brown, B. T. Davis, T. G. Halsall, and A. R. Hands, *J. Chem. Soc.* p. 4492 (1962).

²²¹ B. T. Davis, T. G. Halsall, and A. R. Hands, *Proc. Chem. Soc.* p. 83 (1961).

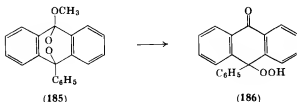
²²² C. Dufraisse, *Bull. Soc. Chim. France* **53**, 823 (1933).

²²³ L. Enderlin, *Ann. Chim. (Paris)* **10**, 5 (1938).

²²⁴ A. Mustafa, *J. Chem. Soc.* p. 1662 (1949).

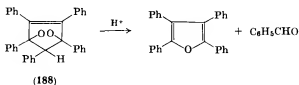
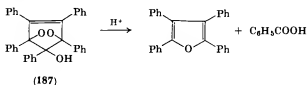
²²⁵ C. Pinazzi, *Compt. Rend.* **225**, 1012 (1947).

²²⁶ C. Dufraisse, A. Étienne, and J. Rigaudy, *Bull. Soc. Chim. France* **15**, 804 (1948).



Anthracene peroxide reacts with concentrated hydrochloric acid to give 9-oxo-10-chloroanthracene, while the reaction with hydrobromic acid gives either 9-oxo-10-bromoanthracene or 9,10-dibromo-9,10-dihydroanthracene, depending on the reaction conditions.²²⁷

Cleavage of the endoperoxide (187) by either acid or heat leads to tetraphenylfuran and benzoic acid.²²⁸ Another example of this interesting reaction is the acid hydrolysis of the endoperoxide (188), which gives tetraphenylfuran and benzaldehyde.²²⁹ The course of these two reactions is not yet certain.



Rubrene peroxide (164) gives 189 with magnesium iodide which probably acts as a mild Lewis acid.²³⁰ Cyclic peroxides containing a hydrogen atom on the C atom carrying the O—O group are decomposed by bases in accordance with the Kornblum-de la Mare mechanism [Eq. (14)].²³¹

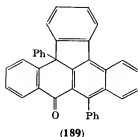
²²⁷ C. Dufraisse and M. Gerard, *Compt. Rend.* **202**, 1859 (1936).

²²⁸ G. Rio and A. Ranjon, *Compt. Rend.* **248**, 111 (1959).

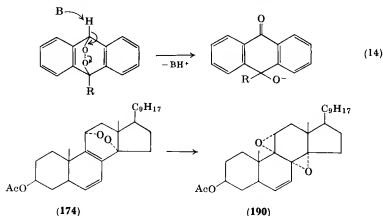
²²⁹ C. Dufraisse, A. Étienne, and J. Aubry, *Compt. Rend.* **239**, 1170 (1954).

²³⁰ C. Dufraisse, A. Étienne, and J. Perronnet, *Compt. Rend.* **241**, 142 (1955).

²³¹ N. Kornblum and H. E. de la Mare, *J. Am. Chem. Soc.* **73**, 880 (1951).



This reaction was studied for many steroid peroxides²³²⁻²³⁵ and for acene peroxides.^{236, 237} However, the action of organic bases such as pyridine or triethylamine on **174** led to a diepoxide (**190**).²¹²



Bladon²³⁸ reported the decomposition of lumisteryl acetate β -peroxide with bases. This reaction is thought to proceed via an intermediate in which a new peroxide bridge is formed in ring A.

3. Thermal Decomposition

The meso-substituted acene peroxides are characterized by their ability to liberate oxygen when heated, with reformation of the stable

²³² R. N. Moore and R. V. Lawrence, *J. Am. Chem. Soc.* **80**, 1438 (1958).

²³³ R. N. Moore and R. V. Lawrence, *J. Am. Chem. Soc.* **81**, 458 (1959).

²³⁴ W. H. Schuller, R. N. Moore, and R. V. Lawrence, *J. Am. Chem. Soc.* **82**, 1734 (1960).

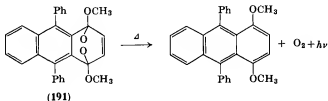
²³⁵ W. H. Schuller and R. V. Lawrence, *J. Am. Chem. Soc.* **83**, 2563 (1961).

²³⁶ C. Dufrasse, G. Rio, and W. A. Burris, *Compt. Rend.* **244**, 2674 (1957).

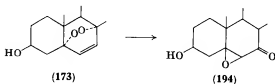
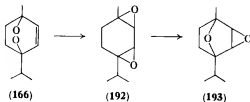
²³⁷ T. G. Halsall, W. J. Rodewald, and P. Willis, *Proc. Chem. Soc.* p. 231 (1958).

²³⁸ P. Bladon, *J. Chem. Soc.* p. 2176 (1955).

aromatic system. The liberation of oxygen is often associated with luminescence. The reaction was first observed with rubrene peroxide (164).¹⁶⁷ 1,4-Dimethoxy-9,10-diphenylanthracene peroxide (191) loses 25% of its peroxide oxygen as O_2 in 10 days at room temperature, whereas at 80° 98% of the peroxide oxygen is given off in 1 hour.¹⁷¹ Thermal decomposition of peroxides without meso substituents leads to quinones.^{169, 239}



The thermal decomposition of ascaridole (166) in xylene results in an oxygen shift to form 193.²⁴⁰⁻²⁴⁴ This isomerization is thought to proceed via the diepoxide (192). A similar isomerization occurs in the thermal decomposition of some steroid peroxides: 194 is formed in 15 % yield when ergosterol peroxide is heated *in vacuo* at 220°.²⁴⁵



²³⁹ A. Étienne, *Compt. Rend.* **218**, 841 (1944).

²⁴⁰ E. K. Nelson, *J. Am. Chem. Soc.* **33**, 1404 (1911).

²⁴¹ E. K. Nelson, *J. Am. Chem. Soc.* **35**, 84 (1913).

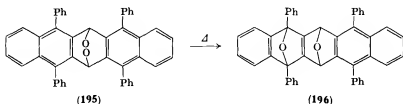
²⁴² H. Thomas and W. Depke, *Arch. Pharm.* **268**, 128 (1930).

²⁴³ F. Richter and W. Presting, *Ber.* **64**, 878 (1931).

²⁴⁴ M. Matić and D. A. Sutton, *J. Chem. Soc.* p. 349 (1953).

²⁴⁵ W. Bergmann and M. B. Meyers, *Ann.* **620**, 46 (1959).

An isomerization of acene peroxide (**195**) into **196** has been described.²⁴⁶



²⁴⁶ A. Étienne and C. Beauvois, *Compt. Rend.* **239**, 64 (1954).

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Monocyclic Sulfur-Containing Pyrones

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I. Introduction

During the last years remarkable advances have been made in the chemistry of thiopyrones, the main types of which are represented by formulas 3-8. The present review reports on the monocyclic sulfur-containing 4*H*-pyran-4-ones (3, 4, 5), types A, and 2*H*-pyran-2-ones (6, 7, 8), types B, which derive from the pyrones (1 and 2), dealing with their synthesis, and their chemical and physical properties.

This review covers the literature available up to the middle of 1965.

In the discussion of the electronic structure, the physical properties, and the chemical reactivity, it seemed appropriate to refer also to

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(A)



(1)



(3)



(4)



(5)



(B)



(2)



(6)



(7)



(8)

some derivatives of benzene and to include some examples where X and Y in A and B do not only represent S or O. For a review of pyrones which do not contain sulfur see Cavalieri.¹

II. Nomenclature

Nonuniformity in nomenclature has often caused confusion. Whereas until recently—especially in the German literature—compounds in which the ring oxygen was replaced by sulfur were designated by “thia,” while the thiocarbonyl group was characterized by the prefix “thio,” nowadays all compounds derived by replacement of oxygen by sulfur take the prefix “thio,” irrespective of whether the ring or the carbonyl oxygen atom has been substituted. Accordingly, 5 should no longer be named thiathio- γ -pyrone, but dithiopyrone-4 or, conforming to IUPAC nomenclature, 4*H*-thiopyran-4-thione.

There are the following differences in nomenclature:

(1)	γ -Pyrone	Pyrone-(4)	4 <i>H</i> -Pyran-4-one
(2)	α -Pyrone	Pyrone-(2)	2 <i>H</i> -Pyran-2-one
(3)	Thia- γ -pyrone	1-Thiopyrone-(4)	4 <i>H</i> -Thiopyran-4-one
(4)	Thio- γ -pyrone	4-Thiopyrone	4 <i>H</i> -Pyran-4-thione
(5)	Thia-thio- γ -pyrone	1,4-Dithiopyrone	4 <i>H</i> -Thiopyran-4-thione
(6)	Thia- α -pyrone	1-Thiopyrone-(2)	2 <i>H</i> -Thiopyran-2-one
(7)	Thio- α -pyrone	2-Thiopyrone	2 <i>H</i> -Pyran-2-thione
(8)	Thia-thio- α -pyrone	1,2-Dithiopyrone	2 <i>H</i> -Thiopyran-2-thione

III. Syntheses

In Tables I–III the sulfur-containing 4*H*-pyran-4-ones (3–5) hitherto reported are listed, and Tables IV–VI contain the corresponding 2*H*-pyran-2-ones (6–8).

¹ L. F. Cavalieri, *Chem. Rev.* **41**, 525 (1947).

TABLE I
4H-THIOPYRAN-4-ONES OF TYPE 3



R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
H	H	H	H	9	PCl ₅	37	110 (CCl ₄)	2, 3
H	H	H	H	1	NaHS	—	—	4, 5
H	H	H	H	5	HgCl ₂ Na ₂ CO ₃	18	110.5–111	6, 7
H	H	H	H	9	Dehydrogenation	—	—	30
H	H	H	H	75	Oxidation	—	—	8
H	H	H	H	3-Carboxyl- 3	—CO ₂	70	110–111.5 (CCl ₄)	9
H	COOCH ₃	H	H	3-Methoxycarbonyl- 9	PCl ₅	19	82–83 (benzene-hexane)	9
H	COOH	H	H	3-Methoxycarbonyl- 3	H ₂ SO ₄	53	185.5–186 (ethanol)	9
H	COOH	H	H	3-Methoxycarbonyl- 9	PCl ₅	29	185.5–186 (ethanol)	9
H	CONH ₂	H	H	3-Methoxycarbonyl- 3	Conc. NH ₃	81	198–198.5 (ethanol)	9

² F. Arndt and N. Bekir, *Ber.* **63**, 2393 (1930).

³ M. Rolla, G. Traverso, and M. Sanesi, *Ann. Chim. (Rome)* **42**, 515 and 673 (1952).

⁴ F. Arndt and E. Aron, *Rev. Fac. Sci. Univ. Istanbul Ser. A.* **13**, 66 (1948); *Chem. Zentr.* **II**, p. 767 (1950).

⁵ R. Mayer, *Chem. Tech. (Berlin)* **10**, 418 (1958).

⁶ G. Traverso, *Ber.* **91**, 1224 (1958).

⁷ G. Traverso, *Ann. Chim. (Rome)* **46**, 821 (1956).

⁸ N. J. Putochin and W. S. Jegorowa, *Dokl. Akad. Nauk. SSSR* **96**, 293 (1954).

⁹ D. S. Tarbell and P. Hoffman, *J. Am. Chem. Soc.* **76**, 2451 (1954).

TABLE I—continued

R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C)(solvent)	Ref.
H	OH	H	H	Carboxylic acid	—	—	87 (subl.)	10
H	OCH ₃	H	H	3-Hydroxy- 3	CH ₃ N ₂	—	82 (subl.)	10
C ₆ H ₅	H	H	H	2-Phenyl- 5	HgCl ₂	15	94-96 (water)	11
CH ₃	H	H	CH ₃	2,6-Dimethyl- 9	PCl ₅ or SO ₂ Cl ₂	—	100-102 (CHCl ₃)	3
CH ₃	H	H	CH ₃	2,6-Dimethyl- 5	HgCl ₂ /Na ₂ CO ₃	10	102.6-103.4 (subl.)	3, 4, 6
CH ₃	H	H	CH ₃	Selenone	H ₂ SO ₄	—	103 (subl.)	7
CH ₃	H	H	CH ₃	Selenone	NH ₂ OH·HCl and hydrolysis	—	104 (subl.)	7
CH ₃	H	H	CH ₃	Type 24	H ₂ S	90	104 (cyclohexane)	12
CH ₃	Cl	H	CH ₃	2,6-Dimethyl- 9	SO ₂ Cl ₂	—	96 (water)	3, 4
C ₆ H ₅	H	H	C ₆ H ₅	2,6-Diphenyl- 9	PCl ₅	15-25	132 (water)	13
C ₆ H ₅	H	H	C ₆ H ₅	2,6-Diphenyl- 5	Oxime or HgCl ₂ /Na ₂ CO ₃	—	132-133 (petr. ether)	13
C ₆ H ₅	H	H	C ₆ H ₅	Type 24	H ₂ S	50	133 (petr. ether)	12
C ₆ H ₅	Cl	H	C ₆ H ₅	2,6-Diphenyl- 9	PCl ₅	—	119-120 (methanol or ligroin)	13
SH	CH ₃	CH ₃	SH	C ₂ H ₅ -CO-C ₂ H ₅	KOH, CS ₂	15	157 (decomp.) (CHCl ₃ /C ₂ H ₅ Br ₂)	14
SCH ₃	CH ₃	CH ₃	SCH ₃	Type 26a	CH ₃ I	64	123 (acetone/water)	14
SC ₆ H ₅	CH ₃	CH ₃	SC ₆ H ₅	Type 26a	C ₂ H ₅ Br	95	70 (ligroin)	14
SCH ₃ C ₆ H ₅	CH ₃	CH ₃	SCH ₃ C ₆ H ₅	Type 26a	C ₆ H ₅ -CH ₂ Cl	79	65.6-66 (ligroin)	14
SCOC ₆ H ₅	CH ₃	CH ₃	SCOC ₆ H ₅	Type 26a	CH ₃ CO CH ₃ CO C ₆ H ₅ -COCl	—	109-112 (decomp.) (ligroin)	14
SCO C ₆ H ₅	CH ₃	CH ₃	SCO C ₆ H ₅	Type 26a	C ₆ H ₅ -COCl	—	105 (ligroin)	14
SH	COOC ₂ H ₅	COOC ₂ H ₅	SH	Type 22	CS ₂ , KOH	41	133 (CHCl ₃ /petr. ether.)	2, 15
SCH ₃	COOC ₂ H ₅	COOC ₂ H ₅	SCH ₃	Type 26a	CH ₃ I	—	82-83 (ethanol)	2, 15
SCH ₃	H	H	SCH ₃	Type 73	Saponification —CO ₂	—	130-131 (water)	2, 15
SO ₂ CH ₃	H	H	SO ₂ CH ₃	Type 73	AcOH/H ₂ O ₂	90	270 (water)	2
SCH ₃	R	R	SCH ₃	—	—	—	—	16
SH	CH ₃	H	SH	C ₂ H ₅ -CO-CH ₃	KOH, CS ₂	—	144.5-145 (acetone/petr. ether)	14

SCH ₃	CH ₃	H	SCH ₃	Type 26a	CH ₃ I	—	89.5 (acetone/water)	14
SCO	CH ₃	H	SCO	Type 26a	CH ₃ CO	—	85.5–86 (ligroin)	14
CH ₃			CH ₃		CH ₃ CO	O		
SH	C ₆ H ₅	C ₆ H ₅	SH	C ₂ H ₇ —CO—C ₆ H ₅	KOH, CS ₂	3	118 CHCl ₃ (petr. ether)	14
SH	C ₆ H ₅	H	SH	C ₆ H ₅ —CH ₂ —CO—CH ₃	KOH, CS ₂	21	146 (acetone/petr. ether)	14
SH	C ₆ H ₅	C ₆ H ₅	SH	C ₆ H ₅ —CH ₂ —CO—CH ₂ —C ₆ H ₅	KOH, CS ₂	47	105 (benzene/ligroin)	14, 17
SCH ₃	C ₆ H ₅	C ₆ H ₅	SCH ₃	Type 26a	CH ₃ I	90	167 (ethanol)	14, 17
SC ₂ H ₅	C ₆ H ₅	C ₆ H ₅	SC ₂ H ₅	Type 26a	C ₂ H ₅ I	63	141.5 (acetone/water)	17
SC ₃ H ₇	C ₆ H ₅	C ₆ H ₅	SC ₃ H ₇	Type 26a	C ₃ H ₇ X (X = Cl, Br, I)	67–84	88 (EtOAc/petr. ether)	17
SCH ₃	C ₆ H ₅	C ₆ H ₅	SCH ₃	Type 26a	C ₆ H ₅ CH ₂ Br	86	131 (acetone/water)	17
SCO	C ₆ H ₅	C ₆ H ₅	SCO	Type 26a	C ₆ H ₅ —COCl	92	142 (EtOAc/petr. ether)	17
SC ₂ H ₅	COOC ₂ H ₅	COOC ₂ H ₅	SC ₂ H ₅	Type 26a	C ₂ H ₅ Br	—	47–49 (ethanol)	15
SCO	COOC ₂ H ₅	COOC ₂ H ₅	SCO	Type 26a	C ₆ H ₅ —COCl	—	128–129 (EtOAc/petr. ether)	15
SCH ₃	COOH	COOH	SCH ₃	Type 26a	CH ₃ I	—	230 (decomp.) (nitrobenzene)	15
SC ₂ H ₅	COOH	COOH	SC ₂ H ₅	Type 26a	C ₂ H ₅ Br	—	178–180	15
SC ₂ H ₅	COOC ₂ H ₅	COOC ₂ H ₅	SC ₂ H ₅	Type 26a	C ₂ H ₅ I	—	47–49 (ethanol)	15
SCH ₃	COOC ₂ H ₅	COOC ₂ H ₅	SCH ₃	Type 26a	C ₂ H ₅ I	—	82–83 (ethanol)	15
SH	COOH	H	SH	Type 26a	HCl/HOAc	—	143 (decomp.) (benzene)	15
SC ₂ H ₅	COOH	H	SC ₂ H ₅	Type 26a	C ₂ H ₅ Br	—	129–131	15
SCH ₃	COOH	H	SCH ₃	Type 26a	CH ₃ I	—	215–216	15
SCH ₃	COOC ₂ H ₅	COOC ₂ H ₅	SCH ₃	Type 26a	(CH ₃) ₂ SO ₄	—	82–83 (methanol)	2

¹⁰ V. Horák and N. Kucharczyk, *Chem. Ind. (London)* p. 694 (1960).

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¹² F. G. Bardone, *Ann. Chim. (Paris)* [13] **3**, 52 (1958); *Chem. Zentr.* 13763 (1958).

¹³ F. Arndt, P. Nachtwey, and J. Pusch, *Ber.* **58**, 1633 (1925).

¹⁴ H. Apitzsch, *Ber.* **38**, 2888 (1905).

¹⁵ H. Apitzsch, *Ber.* **41**, 4028 (1908).

¹⁶ V. Horák, J. Zavada, and Á. Piskala, *Acta Chim. Acad. Sci. Hung.* **21**, 97 (1959).

¹⁷ H. Apitzsch, *Ber.* **37**, 1599 (1904).

TABLE I—continued

R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
SCH ₃	COOC ₂ H ₅	COOH	SCH ₃	Type 73	HCl	—	176 (gl. HOAc)	2
SCH ₃	COOH	COOH	SCH ₃	Type 73	HCl	85	243–245 (decomp.) (gl. HOAc)	2
SCH ₃	COOC ₂ H ₅	COOC ₂ H ₅	SCH ₃	Type 26a	CH ₃ N ₃	—	81–82 (ethanol)	18
SH	CONH ₂	CONH ₂	SH	Type 26a	NH ₃ pressure	—	—	15
SCO NH—C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	SCO NH—C ₆ H ₅	Type 26a	C ₆ H ₅ —N—C=O	—	135 (decomp.) (EtOAc/Et ₂ O)	15
SCO NH—C ₆ H ₅	COOC ₂ H ₅	COOC ₂ H ₅	SCO NH—C ₆ H ₅	Type 26a	C ₆ H ₅ —N—C=O	—	140 (acetone/EtOAc)	15
SCH ₂ COOC ₂ H ₅	COOC ₂ H ₅	COOC ₂ H ₅	SCH ₂ COOC ₂ H ₅	Type 26a	Cl—CH ₂ —COOC ₂ H ₅	—	—	15
SO ₂ H	C ₆ H ₅	C ₆ H ₅	SO ₂ H	Type 26a	H ₂ O ₂	—	261	15
SO ₂ CH ₃	C ₆ H ₅	C ₆ H ₅	SO ₂ CH ₃	Type 26a	CH ₃ I	—	190–191 (acetone)	15
SO ₂ C ₂ H ₅	C ₆ H ₅	C ₆ H ₅	SO ₂ C ₂ H ₅	Type 26a	C ₂ H ₅ Br	—	173–174	15
SCH ₃	CH ₃	H	SCH ₃	H ₃ C—S C=C—CO—C=C R' R''	Cyclization	—	90 (ethanol)	19
SCH ₃	C ₂ H ₅	H	SCH ₃	H ₃ C—S C=C—CO—C=C R' R''	Cyclization	—	47–48 (petr. ether)	19
SCH ₃	CH ₃	CH ₃	SCH ₃	H ₃ C—S C=C—CO—C=C R' R''	Cyclization	—	122–123 (EtOAc)	19
SCH ₃	C ₂ H ₅	C ₂ H ₅	SCH ₃	H ₃ C—S C=C—CO—C=C R' R''	Cyclization	—	88 (ethanol)	19
SCH ₃	C ₆ H ₅	C ₆ H ₅	SCH ₃	H ₃ C—S C=C—CO—C=C R' R''	Cyclization	—	166–167 (ethanol)	19

¹⁸ A. Schönberg and W. Asker, *J. Chem. Soc.*, p. 198 (1945).

¹⁹ A. Thuillier and J. Vialle, *Bull. Soc. Chim. France* p. 2182 and 2187 (1962).

TABLE II
4H-PYRAN-4-THIONES OF TYPE 4



R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
H	H	H	H	1	P ₄ S ₁₀	—	47–48.5 49.2–49.5 (ligroin)	20
H	OH	H	H	3-Hydroxy- 1	P ₄ S ₁₀	52	54 (MeOH/ water)	26
H	CH ₃ COO	H	H	3-Hydroxy- 4	CH ₃ COCl	—	48–49 (petr. ether)	26
CH ₃	H	H	CH ₃	2,6-Dimethyl- 1	P ₄ S ₁₀	86	144.2–144.9 145 (<i>i</i> -PrOH)	20, 21
CH ₃	H	H	CH ₃	2,6-Dimethyl- 1	P ₄ S ₁₀	80	145 (methanol)	22
CH ₃	H	H	CH ₃	Pyrylium salt	KHS or Na ₂ S·9H ₂ O (in acetone)	Up to 95	145 (methanol)	7, 23
CH ₃	H	H	CH ₃	Pyrylium salt	NaHS	70–99	148(methanol)	7, 22
CH ₃	H	H	CH ₃	(CH ₃ —CS—CH ₂) ₂ CO	HCl	81	145(methanol)	22
CH ₃	H	H	CH ₃ O	2-Methyl-6-Methoxy- 1	P ₄ S ₁₀	—	106 (ether)	29
CH ₃	H	H	C ₆ H ₅	2-Methyl-6-phenyl- 1	P ₄ S ₁₀	92	116–117 (methanol)	27, 30
CH ₃	H	H	C ₆ H ₅	Pyrylium salt	NaHS	30–94	116 (benzene/ petr. ether)	7

²⁰ F. Arndt, E. Scholz, and P. Nachtwey, *Ber.* **57**, 1903 (1924).

²¹ A. Hantzsch, *Ber.* **52**, 1535 (1919).

²² G. Traverso, *Ann. Chim. (Rome)* **47**, 3 (1957).

²³ H. Kato, T. Ogawa, and M. Ohta, *Bull. Chem. Soc. Japan* **33**, 1467 (1960); *Chem. Zentr.* p. 884 (1963).

TABLE II—continued

R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
CH ₃	H	H	C ₆ H ₅	Selenopyrylium salt	NaHS	65	116 (methanol/ ligroin)	31
CH ₃	COOCH ₃	H	CH ₃	Type 1	P ₄ S ₁₀	46	112 (ligroin)	25
CH ₃	COOC ₂ H ₅	COOC ₂ H ₅	CH ₃	Type 1	P ₄ S ₁₀	—	107–108 (ligroin)	25
C ₂ H ₅	H	H	C ₂ H ₅	2,6-Diethyl- 1	P ₄ S ₁₀	—	45 (petr. ether)	24, 25
C ₂ H ₅	H	H	C ₂ H ₅	Type 23	P ₄ S ₁₀	31	45 (petr. ether)	24
C ₆ H ₅	H	H	H	2-Phenyl- 1	P ₄ S ₁₀	—	83 (petr. ether)	27
C ₆ H ₅	H	H	H	Pyrylium salt	NaHS	51–68	83 (petr. ether)	7
C ₆ H ₅	H	H	COOC ₂ H ₅	2-Phenyl-6-ethoxy-carbonyl- 1	P ₄ S ₁₀	94	129 (ethanol)	11
C ₆ H ₅	H	H	C ₆ H ₅	2,6-Diphenyl- 1	P ₄ S ₁₀	—	170.5–173 (ethanol)	20
C ₆ H ₅	H	H	C ₆ H ₅	Pyrylium salt	NaHS	44	170–171 (ethanol)	7
C ₆ H ₅	H	H	C ₆ H ₅	Thiopyrylium salt	NaHS	46	170–171 (ethanol)	7
C ₆ H ₅	H	H	C ₆ H ₅	Selenopyrylium salt	NaHS	—	172 (ethanol)	31
C ₆ H ₅	H	H	<i>p</i> -CH ₃ —C ₆ H ₄	Type 1	P ₄ S ₁₀	—	142 (methanol)	30
C ₆ H ₅	H	H	<i>p</i> -CH ₃ O—C ₆ H ₄	Type 1	P ₄ S ₁₀	—	185–186 (benzene/ petr. ether)	30
C ₆ H ₅	COOC ₂ H ₅	COOC ₂ H ₅	C ₆ H ₅	Type 1	P ₄ S ₁₀	—	148, 149 (methanol)	25
C ₆ H ₅	H	H	<i>p</i> -Cl—C ₆ H ₄	Type 1	P ₄ S ₁₀	—	156 (ethanol)	30

C_6H_5	H	H	$p\text{-Br}-C_6H_4$	Type 1	P_4S_{10}	—	170–172 (CCl_4)	30
$COOC_2H_5$	H	H	H	2-Ethoxycarbonyl-1	P_4S_{10}	—	66–67 (petr. ether)	24
$COOC_2H_5$	H	H	$COOC_2H_5$	2,6-Diethoxycar- bonyl- 1	P_4S_{10}	—	51 (petr. ether)	28
$COOC_2H_5$	H	H	$COOC_2H_5$	Type 23	P_4S_{10}	—	51 (petr. ether)	28
$COOC_2H_5$	OH	H	$COOC_2H_5$	2,6-Diethoxycarbonyl- 3-hydroxy- 1	P_4S_{10}	90	88 (ethanol)	26
$COOC_2H_5$	H	OH	H	2-Ethoxycarbonyl-5- acetoxy- 4	Acid	—	100 (water)	26
$COOC_2H_5$	H	OH	H	2-Ethoxycarbonyl-5- hydroxy- 1	P_4S_{10}	92	104 (ethanol)	26
$COOC_2H_5$	H	CH_3COO	H	2-Ethoxycarbonyl-5- hydroxy- 4	CH_3COCl	—	56–57 (methanol)	26
$COOC_2H_5$	H	CH_3COO	H	2-Ethoxycarbonyl-5- acetoxy- 1	P_4S_{10}	—	55 (methanol)	26
$COOC_2H_5$	H	C_6H_5COO	H	2-Ethoxycarbonyl-5- hydroxy- 4	C_6H_5COCl	—	98 (methanol)	26
CH_2OCOCH_3	H	OH	H	Type 1	P_4S_{10}	49	114–115 (CCl_4)	26
CH_2OCOCH_3	H	CH_3COO	H	5-Hydroxy-Type 4	CH_3COCl	—	76–77 (petr. ether)	26
$p\text{-CH}_3O-C_6H_4$	H	H	$p\text{-CH}_3O-C_6H_4$	Type 1	P_4S_{10}	—	185 (benzene/ petr. ether)	30
$p\text{-CH}_3O-C_6H_4$	H	H	$p\text{-CH}_3O-C_6H_4$	Type 1	Via dichloride with CH_2COSH	—	185 (benzene/ petr. ether)	32

²⁴ G. Traverso, *Ann. Chim. (Rome)* **45**, 657 (1955).

²⁵ G. Traverso, *Ann. Chim. (Rome)* **45**, 695 (1955).

²⁶ F. Eiden, *Arch. Pharm.* **292/64**, 153 and 461 (1959); *Arzneimittel-Forsch.* **10**, 947 (1960).

²⁷ G. Traverso and M. Sanesi, *Ann. Chim. (Rome)* **43**, 795 (1953).

²⁸ F. Arndt and P. Nachtwey, *Ber.* **56**, 2406 (1923).

²⁹ F. Arndt and S. Avan, *Ber.* **84**, 343 (1951).

³⁰ I. El-Sayed El-Kholy, F. Kamel Rafia, and G. Soliman, *J. Chem. Soc.* p. 2588 (1959); p. 4490 (1961).

³¹ G. Traverso, *Ann. Chim. (Rome)* **47**, 1244 (1957).

³² A. Schönberg, M. Elkaschef, M. Nosseir, and M. M. Sidky, *J. Am. Chem. Soc.* **80**, 6312 (1958).

TABLE III
4*H*-THIOPYRAN-4-THIONES OF TYPE 5



R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
H	H	H	H	4	KSH	—	48 (ligroin)	4
H	H	H	H	3	P ₄ S ₁₀	87	46.2–46.6 (petr. ether)	6
H	H	H	H	Thiopyrylium salt	KSH	89	46.2–46.6 (petr. ether)	6
CH ₃	H	H	CH ₃	2,6-Dimethyl- 4	KSH, or Na ₂ S	About 50	114.2–114.8, 116–117 (ligroin)	4
CH ₃	H	H	CH ₃	Selenone	NaSH	60	114–115 (ligroin)	22
CH ₃	H	H	CH ₃	Pyrylium salt	KSH, Na ₂ S	94	114–115 (ligroin)	23
CH ₃	H	H	CH ₃	Thiopyrylium salt	NaSH	—	114–115 (ligroin)	7
CH ₃	H	H	CH ₃		KSH, Na ₂ S	66	114–115 (ligroin)	11
CH ₃	H	H	CH ₃	2,6-Dimethyl- 3	P ₄ S ₁₀	68	115 (cyclohexane)	12

C ₆ H ₅	H	H	C ₆ H ₅	2,6-Diphenyl- 3	P ₄ S ₁₀	—	129-129.5 129-130 (methanol)	116
C ₆ H ₅	H	H	C ₆ H ₅	2,6-Diphenyl- 4	KSH	85	129 (methanol)	27
C ₆ H ₅	H	H	C ₆ H ₅	Selenone	NaSH	45	129 (methanol)	31
C ₆ H ₅	H	H	C ₆ H ₅	Pyrylium salt	NaSH	—	131 (methanol)	31
C ₆ H ₅	H	H	H	2-Phenyl- 3	P ₄ S ₁₀	—	79-80 (petr. ether)	11
C ₆ H ₅	H	H	H	2-Phenyl-6-carboxy- 5	-CO ₂	37	79-80 (petr. ether)	11
C ₆ H ₅	H	H	H	2-Phenyl-6-carboxy- 5	-CO ₂	—	79-80 (petr. ether)	28
C ₆ H ₅	H	H	COOH	Type 21	KSH then HCl	63	155-160 (decomp.) (ethanol)	11
C ₆ H ₅	H	H	COOH	2-Phenyl-6-carboxy- 5, potassium salt	HCl	—	155-160 (decomp.) (ethanol)	21
C ₆ H ₅	Cl	H	C ₆ H ₅	2,6-Diphenyl-3-chloro-3	P ₄ S ₁₀	—	155 (ethanol)	116
CH ₃	H	H	C ₆ H ₅	Type 21	By recrystallization	—	74-75 (MeOH/ water)	27
CH ₃	H	H	C ₆ H ₅	2-Methyl-6-phenyl- 4	KSH	—	75-76 (ligroin)	24, 27
CH ₃	COOCH ₃	H	CH ₃	2,6-Dimethyl-3-methoxy- carbonyl- 4	KSH	37	84-85 (ligroin)	25
CH ₃	COOC ₂ H ₅	COOC ₂ H ₅	CH ₃	Type 4	KSH	—	99-100 (ligroin)	25
C ₂ H ₅ S	H	H	C ₂ H ₅ S	22	P ₄ S ₁₀	4	93 (ethanol)	19
CH ₃ S	CH ₃	CH ₃	CH ₃ S	2,6-bis(Methylmercapto)- 3,5-dimethyl- 3	P ₄ S ₁₀	—	179-180 (ligroin)	19

TABLE IV
2H-THIOPYRAN-2-ONES OF TYPE 6



R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
H	H	H	H	8	HgCl ₂ /Na ₂ CO ₃	8	18–20	33
H	C ₆ H ₅	H	C ₆ H ₅	4,6-Diphenyl- 8	Ag ₂ CO ₃	75	101	34
H	C ₆ H ₅	H	C ₆ H ₅	2-Chloro-4,6-diphenyl-thiopyrylium chloride	Pb(CH ₃ COO) ₂	30–40	101	34
H	C ₆ H ₅	H	C ₆ H ₅	2-Bromo-4,6-diphenyl-thiopyrylium bromide	Hydrolysis, alcoholysis	20	101	34
CN	C ₆ H ₅	H	CH ₃ S	Type 8	Hydrolysis	35	199 (propanol)	35, 36
CN	C ₂ H ₅	CH ₃	CH ₃ S	Type 8	Alkali methylation	68	125 (ethanol)	35, 36
CN	C ₂ H ₅	CH ₃	C ₃ H ₇ S	Type 8	Hydrolysis, alkylation	50	79 (ethanol)	35, 36
COOCH ₃	C ₆ H ₅	H	CH ₃ S	Type 8	Hydrolysis, alkylation	50	109 (propanol)	35, 36
COOC ₂ H ₅	C ₆ H ₅	H	C ₆ H ₅	Type 33	—	—	—	37

³³ R. Mayer, *Ber.* **90**, 2362 (1957).

³⁴ R. Mayer and G. Speyer, unpublished material, 1964.

³⁵ K. Gewald, Habilitationsschrift, Technische Universität, Dresden, 1964.

³⁶ K. Gewald, *J. Prakt. Chem.* **31**, 205 (1966).

³⁷ D. Leaver, D. M. McKinnon, and W. A. H. Robertson, *J. Chem. Soc.* p. 32 (1965).

TABLE V
2H-PYRAN-2-THIONES OF TYPE 7



R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
H	H	H	H	2	P ₄ S ₁₀	60-80	49-50 (H ₂ O/ EtOH)	38
OH	H	H	H	3-Hydroxy- 2	P ₄ S ₁₀	11	62	39
H	H	COOCH ₃	H	5-Methoxycarbonyl- 2	P ₄ S ₁₀	—	94-95	40
H	H	COOC ₂ H ₅	H	5-Ethoxycarbonyl- 2	P ₄ S ₁₀	—	56-58	40
H	C ₆ H ₅	H	C ₆ H ₅	4,6-Diphenyl- 2	P ₄ S ₁₀	—	121-122 (ethanol)	41
H	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	4,5,6-Triphenyl- 2	P ₄ S ₁₀	—	218 (benzene/ petr. ether)	30
H	C ₆ H ₅	CH ₃ —O	C ₆ H ₅	4,6-Diphenyl-5-methoxy- 2	P ₄ S ₁₀	—	150 (benzene/ petr. ether)	30
H	C ₆ H ₅	CH ₃ —O	<i>p</i> -CH ₃ —C ₆ H ₄	Type 2	P ₄ S ₁₀	—	165 (benzene/ petr. ether)	30

TABLE V—continued

R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
H	C ₆ H ₅	CH ₃ —O	<i>p</i> -CH ₃ O—C ₆ H ₄	Type 2	P ₄ S ₁₀	—	174 (benzene/ petr. ether)	30
H	<i>p</i> -CH ₃ O—C ₆ H ₄	CH ₃ —O	<i>p</i> -CH ₃ O—C ₆ H ₄	Type 2	P ₄ S ₁₀	—	183 (benzene/ petr. ether)	30
H	C ₆ H ₅	C ₆ H ₅ —O	C ₆ H ₅	Type 2	P ₄ S ₁₀	—	192 (benzene/ petr. ether)	30
H	C ₆ H ₅	C ₆ H ₅ —O	<i>p</i> -CH ₃ O—C ₆ H ₄	Type 2	P ₄ S ₁₀	—	185 (benzene/ petr. ether)	30
H	C ₆ H ₅	<i>p</i> -CH ₃ —C ₆ H ₄ —O	C ₆ H ₅	Type 2	P ₄ S ₁₀	—	143 (benzene/ petr. ether)	30
H	C ₆ H ₅	<i>p</i> -Cl—C ₆ H ₄ —O	C ₆ H ₅	Type 2	P ₄ S ₁₀	—	177 (benzene/ petr. ether)	30
H	C ₆ H ₅	<i>p</i> -Br—C ₆ H ₄ —O	C ₆ H ₅	Type 2	P ₄ S ₁₀	—	180 (benzene/ petr. ether)	30

³⁸ R. Mayer and P. Fischer, *Ber.* **95**, 1307 (1962).³⁹ R. Mayer and W. Broy, unpublished material, 1963.⁴⁰ V. Prey, B. Kerres, and H. Berbalk, *Monatsh. Chem.* **91**, 774 (1960).⁴¹ F. Arndt and B. Eistert, *Ber.* **58**, 2318 (1925).

TABLE VI
2H-THIOPYRAN-2-THIONES OF TYPE 8



R	R'	R''	R'''	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
H	H	H	H	15	S ₈	20-28	57-58 (ethanol)	33
H	H	H	H	16	S ₈	20	57-58 (ethanol)	38
H	H	H	H	7	KSH	15	50	38
H	H	H	H	Type 31	CS ₂	1	64 (subl.)	42, 43
H	H	H	H	Type 32	CS ₂	10	64 (subl.)	43
CH ₃	H	CH ₃	H	Type 31	CS ₂	50	99 (ethanol)	43
CH ₃	H	CH ₃	H	Type 32	CS ₂	60	99-100 (ethanol)	44
C ₂ H ₅	H	C ₂ H ₅	H	Type 31	CS ₂	50	kpe, 1 132-134; 114-115 (methiodide)	43
C ₂ H ₅	H	C ₂ H ₅	H	Type 32	CS ₂	40-60	114-115 (methiodide)	43, 44
n-C ₅ H ₁₁	H	n-C ₅ H ₁₁	H	Type 31	CS ₂	40	kpe, 5 160	43
n-C ₅ H ₁₁	H	n-C ₅ H ₁₁	H	Type 32	CS ₂	37-45	kpe, 5 160	44
n-C ₆ H ₁₃	H	n-C ₆ H ₁₃	H	1-Piperidinooctene- 1	CS ₂	—	—	45
C ₆ H ₅	H	C ₆ H ₅	H	Type 31	CS ₂	60	82-85; 172-173 (methiodide)	43
H	CH ₃	H	CH ₃	Type 30	CS ₂	—	—	46
H	C ₆ H ₅	H	C ₆ H ₅	Type 30	CS ₂	30-85 according to the amine	121-122 122-123 123 (dioxane/MeOH)	44 47 42
H	C ₆ H ₅	H	C ₆ H ₅	Ketimine of acetophenone	CS ₂	—	123	43
H	C ₆ H ₅	H	C ₆ H ₅	2-Chloro-4,6-diphenyl- thiopyrylium chloride	H ₂ S C ₂ H ₅ OH H ₂ O pyridine/S ₈	67 10 32 90	123 123 123 123	34

⁴² R. Mayer and J. Wehl, *Angew. Chem.* **77**, 261 (1965).

⁴³ R. Mayer and G. Laban, unpublished material, 1965.



⁴⁴ R. Mayer and H. Lange, unpublished material, 1965.

⁴⁵ R. Mayer and J. Wehl, unpublished material, 1964.

⁴⁶ R. Mayer and B. Neumann, unpublished material, 1964.

⁴⁷ R. Mayer and M. Wirth, unpublished material, 1965.

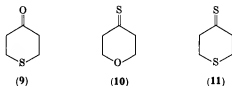
TABLE VI—continued

R	R'	R*	R*	Starting material	Method	Yield (%)	Melting point (°C) (solvent)	Ref.
H	C ₆ H ₅	H	C ₆ H ₅	2-Bromo-4,6-diphenyl-thiopyrylium bromide	H ₂ S C ₆ H ₅ OH H ₂ O pyridine/S ₈	54 5 30 82	123 123 123 123	34
H	C ₆ H ₅	H	C ₆ H ₅	Type 6	P ₄ S ₁₀	82	123	37
H	C ₆ H ₅	H	C ₆ H ₅	34	CH ₃ -CO-SH	—	123	48
H	<i>p</i> -CH ₃ -C ₆ H ₄	H	<i>p</i> -CH ₃ -C ₆ H ₄	1-Morpholino-1-(<i>p</i> -methylphenyl)ethylene	CS ₂	40	162-163 (ethanol)	47
H	<i>p</i> -C ₆ H ₅ -C ₆ H ₄	H	<i>p</i> -C ₆ H ₅ -C ₆ H ₄	1-Morpholino-1-(<i>p</i> -ethylphenyl)ethylene	CS ₂	10	98-99 (ethanol)	47
H	<i>p</i> -CH ₃ O-C ₆ H ₄	H	<i>p</i> -CH ₃ O-C ₆ H ₄	1-Morpholino-1-(<i>p</i> -methoxyphenyl)ethylene	CS ₂	52	149-150 (ethanol)	47
H	<i>p</i> -Cl-C ₆ H ₄	H	<i>p</i> -Cl-C ₆ H ₄	1-Morpholino-1-(<i>p</i> -chlorophenyl)ethylene	CS ₂	26	202-203 (ethanol)	47
H	<i>p</i> -Br-C ₆ H ₄	H	<i>p</i> -Br-C ₆ H ₄	1-Morpholino-1-(<i>p</i> -bromophenyl)ethylene	CS ₂	17	220-221 (ethanol)	47
H	<i>p</i> -C ₆ H ₄ -C ₆ H ₄	H	<i>p</i> -C ₆ H ₄ -C ₆ H ₄	1-Morpholino-1-(<i>p</i> -phenylphenyl)ethylene	CS ₂	—	194	47
CH ₃	C ₆ H ₅	CN	NH ₂	(C ₂ H ₅) ₂ C=C-CN CN	CS ₂	70	171-173 (decomp.) (ethanol)	35, 36
H	C ₆ H ₅	CN	NH ₂	C ₆ H ₅ -C=C-CN CH ₃ CN	CS ₂	60	266-268 (propanol)	35, 36
H	C ₆ H ₅	COOCH ₃	NH ₂	C ₆ H ₅ -C=C-COOCH ₃ CH ₃ CN	CS ₂	65	206-208 (methanol)	35, 36
—(CH ₂) ₂ —		CN	NH ₂		CS ₂	57	253 (propanol)	35, 36
—(CH ₂) ₄ —		CN	NH ₂		CS ₂	85	270-272 (propanol)	35, 36
CN	C ₆ H ₅	CH ₃	CH ₃ S	Type 6	P ₄ S ₁₀	48	142-143 (propanol)	35, 36

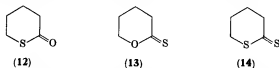
⁴⁸ H. Behringer and A. Grimm, *Ann.* **682**, 188 (1965).

A. DEHYDROGENATION

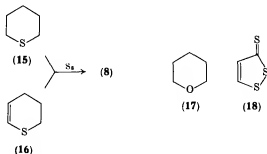
Among the tetrahydro compounds of the 1,4 series, types **9–11**, which are appropriate for dehydrogenation, only derivatives of **9** are easily accessible or commercially available. However, the saturated thioketones (**10** and **11**) have also recently been prepared in the monomeric form.⁴⁹ The stable ketones (**9**) can be dehydrogenated by



PCl_5 , SO_2Cl_2 , or catalytically. Thus, 2,6-diphenylthiopyrone and the parent compound (**3**) were prepared for the first time by dehydrogenation of the corresponding tetrahydro derivatives (**9**) with PCl_5 ,^{2, 3, 13} and 2,6-dimethylthiopyrone was made using SO_2Cl_2 .^{3, 4} Both these reagents give rise to chlorine-containing by-products;^{3, 4, 13} furthermore, yields are reproducible only with difficulty. In our experience³⁹ catalytic dehydrogenation, which so far has been only scantily investigated, should be more promising, since efficient sulfur-resistant dehydrogenation catalysts are now available.



In the 1,2 series, compounds **12–14** and substituted derivatives are known and sometimes easily obtainable, but to date nothing has



⁴⁹ R. Mayer, unpublished material, 1964.

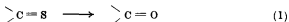
been reported on their dehydrogenation. Thiopyran-2-thione (8) was first prepared by dehydrogenation of thiacyclohexane (15) or thiacyclohexene (16) with sulfur.^{33,38} Corresponding experiments⁴⁹ in the oxygen-containing series (17) did not yield 7, but instead 1,2-dithiol-3-thione (18) with cleavage of the carbon skeleton.

B. REPLACEMENT OF THE RING OXYGEN OF PYRONES BY SULFUR

In pyrones of the types 1, 4 and 7, the ring oxygen can be replaced by sulfur, and so it is possible to prepare thiopyrones 3, 5, or 8. This replacement can succeed well using KSH or NaSH if the working conditions are carefully controlled. It has been employed for the synthesis of thiopyran-4-ones (3) starting from the pyrones (1)^{5, 33, 50} or for the preparation of the dithiopyrones (5) from pyran-4-thiones (4).^{3, 4, 6, 7} The mechanism has not been investigated, but evidently the replacement is possible because in this series the compounds containing sulfur in the ring are more alkali-resistant than the corresponding pyrones with oxygen-containing rings. For the complex conditions and on side reactions see particularly Ref. 6; for rearrangements in the 1,2 series see Refs. 41, 51, and 52. As a rule this replacement is an equilibrium reaction, and so the ring sulfur can in principle be replaced by oxygen. The substituents in the 2- and 6-positions of the 4*H*-thiopyran-4-thiones contribute to the polarization of the C—S—C bonds and seem to affect the reaction significantly.⁷

C. REPLACEMENT OF THE SULFUR ATOM OF THE THIOCARBONYL GROUP BY OXYGEN

Transformation of a thione into a carbonyl group [Eq. (1)] is today a standard technique in sulfur chemistry and generally proceeds in very good yields with widely different classes of compounds. Efficient methods are based on hydrolysis, alcoholysis, or oxidation. Hydrolysis involves nucleophilic attack at the thiocarbonyl group, followed by elimination of H₂S [Eq. (2)]. Factors tending to shift the equilibrium

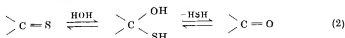


⁵⁰ P. L. Pauson, G. R. Proctor, and W. J. Rodger, *J. Chem. Soc.* p. 3037 (1965).

⁵¹ I. El-Sayed El-Kholy and F. Kamel Rifa, *J. Chem. Soc.* p. 5297 (1962).

⁵² W. Broj and R. Mayer, *Z. Chem.* **3**, 150 (1963).

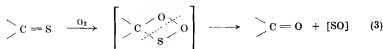
towards the ketone therefore have a favorable influence. In practice water is not used by itself, but (according to the stability of the system) together with acids, Lewis acids (e.g., via Hg adducts), bases, or "sulfur-capturers" (e.g., HgO, Ag₂CO₃). A sulfur-capturer is also used during alcoholysis.



In the pyrone series this hydrolysis of the thione sulfur is a general reaction and the efficiency of the method is demonstrated by the many examples in the tables. The Hg adducts should be prepared first and then decomposed in an alkaline medium, such as sodium hydrogen carbonate solution.^{3, 4, 6, 11, 13} In this way the parent compounds **3** and **6** became accessible, starting from **5** and **8**.^{33, 38, 53}

A selenone group can also be hydrolyzed to a carbonyl, as for example in 4*H*-thiopyran-4-selenone.³¹ On the formation of the C=O group by the action of hydrazine or hydroxylamine upon thiopyrones containing C=S groups see below and Ref. 30.

The oxidation by oxygen, or an inorganic or organic oxidizing agent, may, among other modes of attack, involve a direct addition of oxygen at the thione with splitting off of (SO)_n (see Refs. 54 and 55)



[Eq. (3)]. Due to side reactions the oxidative removal of sulfur from thiopyrones is of only small synthetic importance. Occasionally, e.g., with 2,6-diaryl-substituted compounds, the replacement of the sulfur of the thiocarbonyl group by oxygen on melting 4*H*-pyran-4-thiones in a current of air has been observed.⁵⁶ During cautious oxidation of 2*H*-pyran-2-thiones (**7**) with H₂O₂/glacial acetic acid the corresponding oxygen-containing pyrones are also formed. Since the 1,2-dithiopyrone system (**8**) is synthetically more easily available than the corresponding oxygen-containing compound, in this particular series the transformation C=S → C=O is of real synthetic value.

⁵³ R. Mayer, *Ber.* **90**, 2369 (1957).

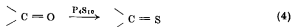
⁵⁴ R. Mayer and J. Orgis, unpublished material, 1964.

⁵⁵ Concerning [SO] see P. W. Schenk and R. Steudel, *Angew. Chem.* **77**, 437 (1965).

⁵⁶ M. El-Kaschef and M. H. Nosseir, *J. Chem. Soc.* p. 4643 (1963).

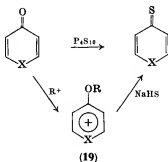
D. TRANSFORMATION OF THE CARBONYL INTO THE THIOCARBONYL GROUP

In the 1,4 as well as in the 1,2 series the replacement of the carbonyl oxygen for sulfur by the aid of P_4S_{10} or analogous sulfides of phosphorus is well-proved, though this procedure is not generally applicable⁵⁷ [Eq. (4)]. As may be seen from the tables, the experimental



work in this field has recently increased considerably. As a rule, however, the original method is followed and the preparations are carried out in a nonpolar solvent above 100° . Yields are variable; their average, however, lies above 40%. In this manner not only have the parent compounds **4** (from **1**),²⁰ **5** (from **3**),⁶ and **7** (from **2**)³⁸ been synthesized, but also numerous derivatives. 3-Hydroxy-2H-pyran-2-thione³⁹ and other 2H-pyran-2-thiones of type **7** which are otherwise difficult to prepare were made from the corresponding 2H-pyran-2-ones.^{30, 40, 41} Sulfurization of the carbonyl group by P_4S_{10} in the 4H-pyran-4-one or the 4H-thiopyran-4-one series has proved to be of particular efficiency. In this way many derivatives of pyran-4-thione (**4**)^{3, 11, 21, 24, 25, 27-30, 58, 59} and thiopyran-4-thione (**5**)^{4, 12, 13, 27} became available starting from the pyrones and thiopyrones **1** and **3**.

Better yields are often obtained if, instead of sulfurizing the pyrones **1** or **3** with P_4S_{10} , they are transformed into the pyrylium salts (**19**), which subsequently are easily sulfurized by alkali hydrogen sulfides



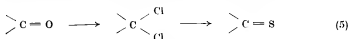
⁵⁷ On simple thiocarbonyl-compounds see R. Mayer, J. Morgenstern, and J. Fabian, *Angew. Chem.* **76**, 157 (1964).

⁵⁸ M. Guthzeit and W. Epstein, *Ber.* **20**, 2111 (1887).

⁵⁹ M. Rolla, M. Sanesi, and G. Traverso, *Ann. Chim. (Rome)* **44**, 430 (1954).

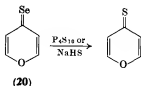
or $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$.^{6, 7, 11, 22, 23, 25, 27, 31} For the reaction conditions see Kato *et al.*²³

For the preparation of diaryl thioketones, the corresponding ketones may be converted into the gem-dichlorides, for instance by SOCl_2 , which then are sulfurized by thioacetic acid⁶⁰ [Eq. (5)]. 2,6-Diaryl-

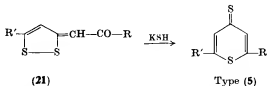


substituted 4*H*-pyran-4-thiones (4) are also obtainable in this way, from the corresponding 4-pyrones.³²

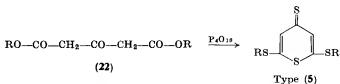
4*H*-Pyran-4-selenones (20), like the corresponding oxygen derivatives (1), can be transformed into 4*H*-thiopyran-4-thiones, using NaSH or P_4S_{10} .^{22, 27, 31}



Sulfurizing of ketones with subsequent cyclization may yield thiopyrones. Thus the oxygen isologs (21) of the so-called thiothiophenes give 4*H*-thiopyran-4-thiones (5)^{7, 11, 31} on treatment with KSH. When $\text{R} = \text{COOH}$, monosubstituted thiopyran-4-thiones became available after decarboxylation.¹¹



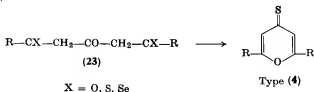
Compounds of type 5 are also formed on reacting acetone dicarboxylic acid esters (22) with P_4S_{10} ,⁶¹ and 4*H*-pyran-4-thiones (4)



⁶⁰ See, *inter alia*, A. Schönberg, O. Schütz, and S. Nickel, *Ber.* **61**, 1375 (1928).

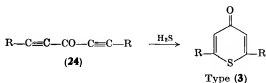
⁶¹ A. Pfister, unpublished material, 1962; see Ref. 19.

are prepared analogously, starting from the appropriate 1,3,5-triketone (23).^{24,39}



E. CYCLIZATION USING H_2S

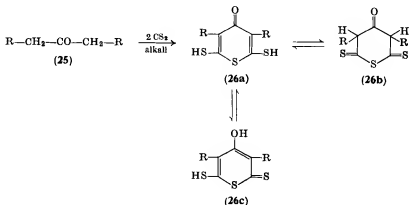
β, β' -Disubstituted diethynyl ketones (24) react with hydrogen sulfide, 2,6-disubstituted 4*H*-thiopyran-4-ones (3) being formed.¹² The starting ketones (24) are readily prepared, and so by this procedure a general method for preparing 2,6-disubstituted thiopyrones (3) is available.



F. CYCLIZATION USING CS_2

1. Action of Carbon Disulfide on Methylene Ketones

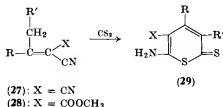
It has been known for a long time that methylene ketones of type 25 yield 4*H*-thiopyran-4-ones (26) on reaction with carbon disulfide in the presence of alkali.^{14,15,17} On the mechanism of this reaction see



Ref. 19, and concerning the tautomerism Refs. 4 and 18. This procedure has been applied successfully to a wide variety of ketones.

2. Action of Carbon Disulfide on CH-Acidic Nitriles

The reaction of carbon disulfide with alkylidene malononitriles (27) or alkylidene cyanoacetic acid esters (28), in dimethyl formamide in the presence of triethylamine, leads to aminodithiopyrones (29) in high yields.^{35, 36} The preparation may also be realized directly,

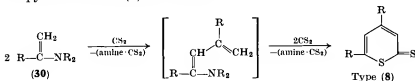


although in diminished yields, starting from the ketones, malononitrile, and CS_2 , and operating in ethanol containing triethylamine. Table VI lists the compounds of type 29 synthesized to date.^{35, 36}

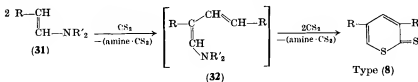
3. Action of Carbon Disulfide on Enamines and Dienamines

Simple α -dithiopyrones (8), until recently hard to prepare and therefore inadequately investigated, are now available by a generally applicable and as a rule very efficient procedure, the one-step reaction of enamines of type 30 or 31 with carbon disulfide.^{42, 43, 46, 47} The reaction should be carried out in a polar solvent at room temperature.

Starting from enamines of methyl ketones (30), 4,6-disubstituted thiopyran-2-thiones (8) are obtained:



Enamines of aldehydes 31 yield 3,5-disubstituted α -dithiopyrones:

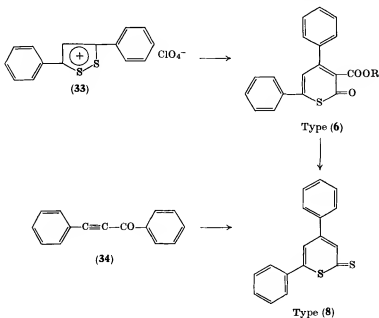


In the case of monomeric aldehyde enamines (31), it was possible to show that the products are formed via the dienamine (32) which can be converted directly with carbon disulfide, requiring a shorter reaction time and giving higher yields.⁴³ Starting from the dienamine (32) (R = H) the parent compound (8) is formed; the yield, however, is maximally about 10%.⁴³

On the use of carbon disulfide for synthesizing sulfur-containing heterocyclic compounds see Mayer and Gewald.⁶² Compounds of type 8 prepared by the procedure described above are listed in Table VI.

G. OTHER METHODS

Two other recently published methods allow the synthesis of 4,6-disubstituted dithiopyrones (8), although the yields are low. The action of nucleophilic agents (e.g., sodiomalonic ester) on 3,5-diphenyl-1,2-dithiolium perchlorate (33) gives thiopyran-2-ones (6), with ring expansion, which may be converted into 4,6-diphenyl-dithiopyrone in the usual way.³⁷ The other method involves the



⁶² R. Mayer and K. Gewald, *Angew. Chem.* (in press).

action of dithioacetic acid on 1-benzoyl-2-phenylacetylene (**34**); the acid acts as both sulfur-donating agent and methylene component.⁴⁸

IV. Properties of Thiopyrones

The properties of pyrones will be dealt with in the following order:

- (A) attempts to characterize the structural types of pyrones;
- (B) physical properties (except for the infrared spectra of pyrones, as they have been recently discussed in detail⁶³;
- (C) chemical reactivity.

The Hückel approximation of the molecular orbital method (HMO method) can be used to interpret and predict the quantities of Sections IV, B, 1-3 from the energies of the molecular orbitals.^{64, 65} The theoretical data for the quantities of Sections IV, B, 4 and 5 are obtainable from the expansion coefficients of the molecular orbitals.

A. ATTEMPTS TO CHARACTERIZE THE STRUCTURAL TYPES OF PYRONES

It is our aim to find certain structural similarities between pyrones and other organic compounds for a better understanding of their physical and chemical properties, and to utilize such similarities in predicting properties not yet studied experimentally. The following consideration relates to compounds of the γ -pyrone type; it is easily extended to α -pyrones.

Quantum chemical calculations indicate a similarity between tropone (**35**) and 4*H*-pyran-4-one (**1**).^{66, 67} Hence, the thiopyrones (**3** and **6**) should show a pseudotropone character, and the thiopyrones (**4**, **5**, **7**, and **8**) may be compared with the tropothione (**36**), which has not yet been synthesized.^{33, 38, 53, 68} The dipolar structures established by Arndt *et al.*²⁰ in 1924 suggest the formal similarity of the

⁶³ A. R. Katritzky and A. P. Ambler, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. 2, p. 253. Academic Press, New York, 1963.

⁶⁴ A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, 1961.

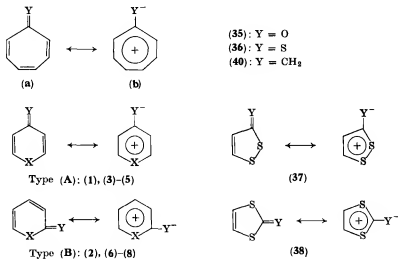
⁶⁵ R. Zahradnik, *Advan. Heterocyclic Chem.* **5**, 1 (1965).

⁶⁶ R. D. Brown, *J. Chem. Soc.* p. 2670 (1951).

⁶⁷ H. J. Dauben, Jr. and H. J. Ringold, *J. Am. Chem. Soc.* **73**, 876 (1951).

⁶⁸ R. Mayer, *Angew. Chem.* **69**, 481 (1957).

type A, B, 37 and 38.³⁸ All are 8π -electron systems isoelectronic with tropone/tropothione. The relation of γ -pyrones (1, 3–5) with fulvenes (39, 40), dioxadiene (41, X=O), and quinone-type compounds (42)



could be illuminating. Fulvenes (Fig. 1) and pyrones are similar in each possessing only one Kekulé structure. Figure 1 indicates schematically these formal relationships. Compounds of type A, 40 and 40a are iso- π -electronic, with a tendency to form a ring π electron sextet.

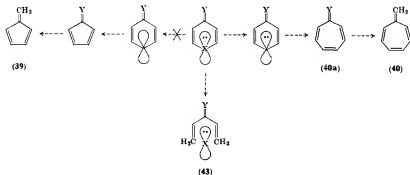
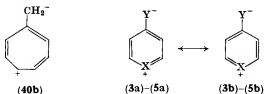


FIG. 1. X and Y denote sulfur or oxygen. The dots in the p_z orbital indicate the number of electrons.

If $X = S$ (3, 5) then, if the hybrid $3pd^2$ sulphur orbitals are assumed to participate in the conjugation, types **A** and **40** are also isoorbital. In heptafulvene, however, the contribution of the ionic structures of type **40b** to its wave function is less significant than the contribution of structures **3a-5a** and **3b-5b** in compounds of the pyrone type. The effect of structures **a** and **b** will be the greater, the lower the electro-negativity of the atom X and the higher the electronegativity of the atom Y . Among the substances investigated, these conditions are



best satisfied by **3**. If X is very electronegative, similarities between the properties and reactivity of the pyrone and the compound **43** formally produced by elimination of the p_z orbital of the atom X from conjugation are to be expected.

The second comparison illustrates the intermediate position of the pyrones between quinones and dioxadiene-type compounds. These systems are formally produced by linking two ethylene molecules by two groups of type $Y=C<$ or $-X-$, where X and Y are sulfur or oxygen (Fig. 2). Systems **41**, **42**, and **A** are iso- π -electronic (eight electrons), but differ in the number of p_z orbitals participating in the conjugation: six, seven, and eight orbitals in **41**, **42**, and **A**, respectively. Whereas compounds of type **41** are strong electron donors (low ionization potential, easily oxidized), the quinones (**42**) are acceptors of electrons (high electron affinity, easily reduced). The molecular orbitals, shown in Fig. 2, reflect this: an antibonding orbital occupied in substance **41**, all bonding orbitals occupied and all antibonding orbitals unoccupied in type **A**, and a bonding orbital unoccupied in **42**. For pyrones, this applies for a wide range of values for the empirical parameters of the p_z orbitals on the atoms X and Y , but for types **41** and **42** only to certain values of the coulomb integrals (for definitions see p. 250),

$$\alpha_X = \alpha + \delta_X \beta, \quad \delta_X < 1 \quad (\text{substances } \mathbf{41})$$

$$\alpha_Y = \alpha + \delta_Y \beta, \quad \delta_Y > 0.5 \quad (\text{substances } \mathbf{42})$$

assuming the standard value of β for all resonance integrals. Consequently, donor-acceptor properties between those characteristic of dioxadiene and quinone are expected for pyrones. Accordingly,

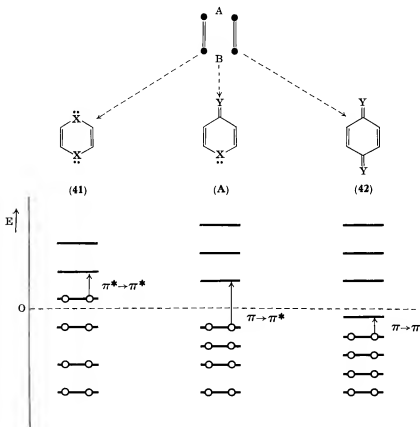


FIG. 2. Energy level diagrams for HMO's. The data are qualitative and valid only for certain empirical parameters of the HMO method.

pyrones should give π complexes with sufficiently strong acceptors, e.g., tetracyanoethylene, but should also be moderately easily reduced. Finally, Fig. 2 shows that the $N \rightarrow V_1$ transitions differ for **41**, type **A**, and **42**, in being $\pi^* \rightarrow \pi^*$, $\pi \rightarrow \pi^*$, and $\pi \rightarrow \pi$, respectively.

B. PHYSICAL PROPERTIES

1. *Electronic Spectra*

The ultraviolet and the visible spectra of pyrones were studied first by Italian authors⁶⁹⁻⁷¹ and later by other investigators.^{37, 72-76} In the absorption curves of α - and γ -pyrones, an $n \rightarrow \pi^*$ band of low intensity usually precedes the intense $\pi \rightarrow \pi^*$ bands. The transitions leading to these bands are schematically illustrated in Fig. 3. Detailed

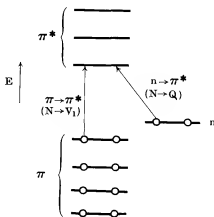


FIG. 3.

data on absorption curves and maxima in various solvents are given in Refs. 33, 70-74 (see also Table VII). Figure 4 shows the absorption curves of γ -pyrones.⁶⁹ The wave numbers of the maxima of the first intense bands are related^{72, 77, 78} to the HMO energies of the $N \rightarrow V_1$ transitions (Fig. 5):

⁶⁹ P. Franzosini, G. Traverso, and M. Sanesi, *Ann. Chim. (Rome)* **45**, 128 (1955).

⁷⁰ M. Rolla and P. Franzosini, *Ann. Chim. (Rome)* **46**, 582 (1956).

⁷¹ P. Franzosini and G. Traverso, *Ann. Chim. (Rome)* **47**, 346 (1957).

⁷² R. Zahradník, C. Párkányi, and J. Koutecký, *Collection Czech. Chem. Commun.* **27**, 1242 (1962).

⁷³ R. Mayer and J. Fabian, unpublished material, 1964.

⁷⁴ P. Given and S. Guha, private communication, 1964.

⁷⁵ G. Pfister-Guillouzo and N. Lozac'h, *Bull. Soc. Chim. France* p. 3254 (1964).

⁷⁶ A. Burawoy, *Ber.* **64**, 462 (1931).

⁷⁷ A. Lüttringhaus and J. Grohmann, *Z. Naturforsch.* **10b**, 365 (1955).

⁷⁸ R. Zahradník and C. Párkányi, *Collection Czech. Chem. Commun.* (in press).

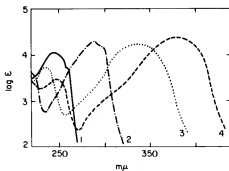


FIG. 4. Absorption curves of 4*H*-pyran-4-one (1), 4*H*-thiopyran-4-one (3), 4*H*-pyran-4-thione (4), and 4*H*-thiopyran-4-thione (5), according to Ref. 69.

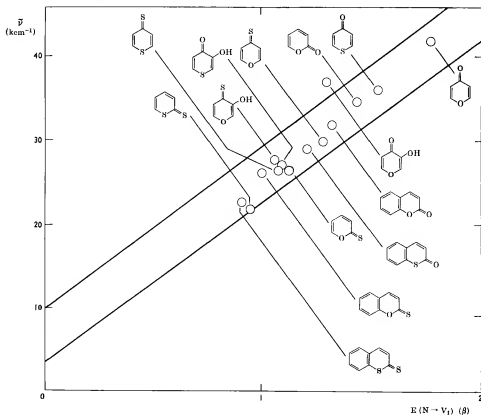


FIG. 5. $\bar{\nu}_{\text{exp}}$ vs $E(N \rightarrow V_1)$ for α - and γ -pyrones and for benzo- α -pyrones, according to Ref. 78.

TABLE VII
ULTRAVIOLET SPECTRA OF PYRONES^a

Compound	Solvent										Shift (mμ) on changing from C ₆ H ₁₂ to H ₂ O ^a	Band character
	Water		Methanol		Ethanol		Dioxane		Cyclohexane			
	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε		
4 <i>H</i> -Pyran-4-one (1)	248	4.10	247 ^c	4.09	246	4.10	242	4.00	238	3.99	+ (10)	N→V ₁
4 <i>H</i> -Thiopyran-4-one (3)	—	—	217 ^c	3.62	218 ^c	3.67	—	—	—	—	—	N→Q ^d
	292	4.21	290 ^c	4.28	290	4.26	—	—	280	4.19	+ (12)	N→V _z
	298	4.18	298 ^c	4.20	298	4.17	287	4.17	318 ^{c,f}	1.72	—	N→Q ^d
4 <i>H</i> -Pyran-4-thione (4)	240	3.80	—	—	236	3.74	235	3.71	230	3.78	+ (10)	N→V _z
	341	4.31	—	—	338	4.24	337	4.21	330	4.22	+ (11)	N→V ₁
	435 ^f	1.93	—	—	466 ^g	1.54	518	1.29	535	1.23	— (100)	N→Q
4 <i>H</i> -Thiopyran-4- thione (5)	—	—	—	—	—	—	—	—	554	1.26	— (119)	—
	254	3.50	—	—	248	3.46	241	3.43	241	3.34	+ (13)	N→V _z
	385	4.40	—	—	384	4.38	381	4.38	371	4.32	+ (14)	N→V ₁
	450 ^g	2.41	—	—	475 ^g	1.84	552	1.56	588 ^g	1.43	— (138)	N→Q
	—	—	—	—	—	—	562	1.56	—	—	—	—
<i>H</i> -Pyran-2-one (2)	—	—	—	—	~ 216 ^a	3.36	—	—	—	—	—	N→V _z ^d
5,6-Dimethyl-2 <i>H</i> - pyran-2-one	—	—	—	—	289 ^a	3.67	—	—	—	—	—	N→V ₁ ^d
	309	3.88	—	—	308	3.78	304	3.92	305	3.66	+ (4)	N→V ₁
2 <i>H</i> -Thiopyran-2- thione (8)	240	4.05	239 ^f	3.89	240	3.99	240	4.00	242	3.98	— (2)	N→V _y
	305	3.91	316 ^f	3.81	315	3.93	318	3.98	319	3.97	— (14)	N→V _z ^d
	400	3.89	430 ⁱ	3.64	407	3.74	413 ^g	3.78	415 ^g	3.62	— (15)	N→V ₁ ^d
	417 ^g	3.86	—	—	426 ^g	3.73	427 ^g	3.76	431 ^g	3.63	— (14)	—
									585 ^g	1.8	—	—

^a A complete summary of the spectral properties is available on request from the authors.

^b + = bathochromic — = hypsochromic, shift.

^c Taken from Ref. 79.

^d Assigned on the band intensity.

^e Measured in hexane.

^f Inflection.

^g Approximate value.

^h Taken from Ref. 86.

ⁱ Taken from Ref. 81.

$$\tilde{\nu}_{\text{exp}}(\text{kcm}^{-1}) = 21.79 E(N \rightarrow V_1) (\beta) + 3.01 \quad (6)$$

(number of substances = 13; correlation coefficient = 0.985). The energies of the $N \rightarrow V_1$ transitions were calculated⁷² for the following values of Coulomb (α_X) and resonance (β_{XY}) integrals:

Parameters 1

Endocyclic atoms	Exocyclic atoms
$\delta_s = 1$	$\delta_s = 0.5$
$\rho_{CS} = 0.7$	$\rho_{CS} = 0.9$
$\delta_o = 2$	$\delta_o = 2$
$\rho_{CO} = 1.1$	$\rho_{CO} = \sqrt{2}$

The quantities δ_X and ρ_{XY} are defined by the equations:

$$\alpha_X = \alpha + \delta_X \beta \quad (7)$$

$$\beta_{XY} = \rho_{XY} \beta \quad (8)$$

where α and β are the Coulomb integral of the $2p_z$ -orbital of carbon and the resonance integral of the carbon-carbon π bond. These values differ somewhat from those employed for calculating indices of chemical reactivity:

Parameters 2

Endocyclic atoms	Exocyclic atoms
$\delta_s = 1$	$\delta_s = 0.5$
$\rho_{CS} = 0.6$	$\rho_{CS} = 0.9$
$\delta_o = 2$	$\delta_o = 2$
$\rho_{CO} = \sqrt{2}$	$\rho_{CO} = \sqrt{2}$

The indices of chemical reactivity were also calculated⁷² using a model with participation in the conjugation of the d orbital of sulfur.⁸² In the calculation, the sulfur orbitals are replaced by two $2p_z$ orbitals (representing the π electron component of ethylene), linked together by a standard bond ($\rho = 1$), but attached to the other part of the molecule by weakened bonds ($\rho_{CS} = 0.6$). The other parameters were as parameters 2.

Parameters 3

Equation (6) can be used as an interpolation formula for estimating the position of the maxima of the first bands for new compounds.

The linear dependence [Eq. (6)] is also satisfied by the data for polynuclear thiopyrones.⁷⁴

Group-symmetry considerations show that for γ -pyrones (C_{2v} symmetry) the $N \rightarrow V_1$ transition is allowed and polarized in the direction of the symmetry axis. Irrespective of the empirical parameters of

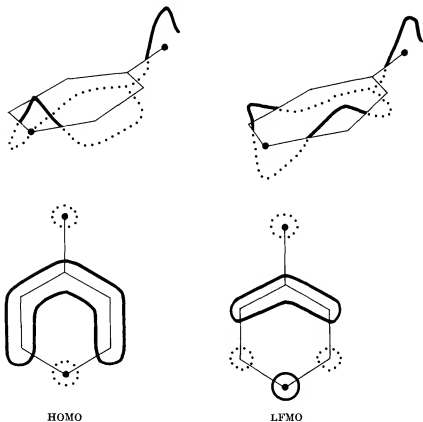


FIG. 6. Two schematic representations of the highest occupied (HOMO) and the lowest unoccupied (LFMO) molecular orbital for compounds of the γ -pyrone type. The positive parts of the MO's are indicated by a full line, the negative parts by a dotted line. Hetero atoms are denoted by heavy dots.

the hetero atoms, both the frontier orbitals (HOMO and LFMO) concerned in the $N \rightarrow V_1$ transition are bilaterally symmetrical with respect to the plane passing through both hetero atoms and are of B_1 type (Fig. 6).

The transition moments Q and the oscillator strengths f for the first intense bands of four γ -pyrones were calculated by means of the HMO method.⁷⁹⁻⁸³

$$Q = \sqrt{2} \cdot \sum_{\mu} c_{1\mu} \cdot c_{-1\mu} \cdot \mathbf{r}_{\mu} \quad (9)$$

$$f = 1.085 \cdot 10^{-6} \bar{\nu}_{\max} \cdot Q^2 \quad (10)$$

where $c_{1\mu}$ ($c_{-1\mu}$) denotes the expansion coefficient in HOMO (LFMO) at the μ th atoms, whose position vector is \mathbf{r}_{μ} , and $\bar{\nu}_{\max}$ is the frequency of the band maximum (cm^{-1}) (Table VIII). The oscillator strengths were not calculated from experimental data, but agreement between theoretical and experimental values is satisfactory, since the molar extinction coefficients exhibit⁷⁰ values exceeding 10^4 .

TABLE VIII

HMO TRANSITION MOMENTS (Q) AND OSCILLATOR STRENGTHS (f) FOR THE FIRST BANDS*

Compound	Q	$\bar{\nu}_{\max}$ (cm^{-1})	f
4 <i>H</i> -Pyran-4-one (1)	1.44	42,000	0.95
4 <i>H</i> -Thiopyran-4-one (3)	1.49	35,700	0.86
4 <i>H</i> -Pyran-4-thione (4)	1.60	30,300	0.84
4 <i>H</i> -Thiopyran-4-thione (5)	1.66	27,000	0.81

* Calculated for data obtained by means of parameters 1.

A successful analysis⁷⁰ of the vibrational structure of the first electronic bands for γ -pyrone and γ -thiapyrone shows that the $0 \rightarrow 0$ transition is forbidden. This is evidently due to the relatively large change in the geometry during the $N \rightarrow V_1$ excitation; bond orders in the ground and excited states indicate significant extension of the ring "double" bonds on passing from the ground state to the excited state since the LFMO exhibits a nodal plane through these bonds (Fig. 6).

⁷⁹ R. Daudel, R. Lefebvre, and C. Moser, "Quantum Chemistry," p. 215. Wiley (Interscience), New York, 1959.

⁸⁰ F. Arndt, G. T. O. Martin, and R. J. Partington, *J. Chem. Soc.* p. 602 (1935).

⁸¹ W. von E. Doering and F. L. Detert, *J. Am. Chem. Soc.* **73**, 876 (1951).

⁸² H. C. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).

⁸³ R. Zahradník and M. Tichý, unpublished material, 1965.

In Fig. 7, the positions of the bands of tropone (**35**)⁸¹ and γ -thiapyrone (**3**)⁷² are indicated on the absorption curve of heptafulvene.⁸⁴ Heptafulvene has been studied by the semiempirical method of limited configuration interaction⁸⁵ (LCI): the first two bands correspond to nearly pure $1 \rightarrow 1'$ and $1 \rightarrow 2'$ transitions. Although the agreement between theory and experiment is probably adversely affected by the use of nonself-consistent MO's in the LCI calculation, a similar assignment may apply to the hetero analogs.

Systematic study^{69, 71} of the influence of substituents at positions 2 and 6 of the pyrone skeleton (Table IX) shows that 2- and 6-methyl

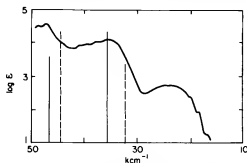


FIG. 7. Absorption curve of heptafulvene⁸⁴ (*n*-hexane) and position of the absorption bands of tropone⁸¹ (isooctane) (-----) and 4*H*-thiopyran-4-one⁷² (cyclohexane) (———).

substituents (except for γ -thiapyrone) merely cause small bathochromic shifts.⁷⁰ The direction of the shift of three of the four substances investigated is not in agreement with the prediction of first-order perturbation treatment.^{86, 87} The bathochromic shift produced by the introduction of phenyl substituents (exception for γ -thiapyrone) is considerably larger than that due to methyl substituents and the same applies to the change in the absorption curves. The effect of carboxyethyl groups has also been studied.⁷¹

Of interest is the study⁸⁸ on the position of the absorption maxima of α -thiathiopyrone (**8**) in 60% HClO_4 ($m\mu$, $\log \epsilon$): 236, 4.49; 267, 3.87; 370, 3.99. The large hypsochromic shift of the first maximum (417 $m\mu$

⁸⁴ W. von E. Doering and D. W. Wiley, *Tetrahedron* **11**, 183 (1960).

⁸⁵ J. Koutecký, P. Hochmann, and J. Michl, *J. Chem. Phys.* **40**, 2439 (1964).

⁸⁶ H. C. Longuet-Higgins and R. G. Sowden, *J. Chem. Soc.* p. 1404 (1952).

⁸⁷ C. A. Coulson, *Proc. Phys. Soc.* **B65**, 933 (1952).

⁸⁸ R. Mayer and R. Bohnensack, unpublished material, 1964.

TABLE IX
INFLUENCE OF METHYL AND PHENYL SUBSTITUENTS ON POSITION AND
INTENSITY OF THE FIRST BANDS^a

Parent skeleton	Position		λ_{\max}	$\log \epsilon$
	2	6		
4 <i>H</i> -Pyran-4-one (1)	—	—	246	4.08
	CH ₃	CH ₃	248	4.15
	Ph	—	277	4.30
	Ph	CH ₃	274	4.32
	Ph	Ph	283-4	4.41
4 <i>H</i> -Thiopyran-4-one (3)	—	—	299	4.20
	CH ₃	CH ₃	297	4.26
	Ph	—	295	4.21
	Ph	Ph	304	4.33
4 <i>H</i> -Pyran-4-thione (4)	—	—	339	4.26
	CH ₃	CH ₃	342	4.36
	Ph	—	363	4.36
	Ph	CH ₃	362-3	4.36
	Ph	Ph	378	4.38
4 <i>H</i> -Thiopyran-4-thione (5)	—	—	381	4.38
	CH ₃	CH ₃	384	4.43
	Ph	—	396	4.86
	Ph	Ph	408	4.36

^a Reprinted by permission from Ref. 69.

in water) is understandable if the absorbing species is a cation formed very probably by protonation on the exocyclic sulfur and approaching in structure to 2-mercaptothiopyrylium (44). The first absorption maximum of thiopyrylium lies at 284 m μ .⁸⁹



2. Donor-Acceptor Properties

These properties have not been investigated experimentally. However, theoretical values of the energies of the highest occupied

⁸⁹ A. Lüttringhaus and N. Engelhard, *Angew. Chem.* **73**, 218 (1961).

(HOMO) and the lowest unoccupied (LFMO) molecular orbitals^{65, 72, 78} indicate that (in agreement with qualitative considerations of the central position of pyrones between dioxadienes and quinones) the α - and γ -pyrones will be neither strong electron donors nor strong acceptors. The replacement of the exocyclic oxygen by sulfur enhances the donor properties. As far as the formation of π complexes is concerned, the pyrones should behave as electron donors; it would be interesting to investigate the spectral properties of pyrone solutions containing a strong acceptor, e.g., tetracyanoethylene.

The pyrones are reduced polarographically.⁹⁰⁻⁹² Four γ -pyrones (1, 3, 4, 5) and α -thiathiopyrone (8)⁹⁰ produced two-electron waves, which probably corresponds to the reduction of the exocyclic bond (however, γ -thiopyrone gives a six-electron wave). No relation was found between the half-wave potentials (Table X) and the LFMO

TABLE X
HALF-WAVE POTENTIALS OF PYRONES⁹⁰

Compound	$E_{1,2}(V)$, NCE	
	0.05 N HCl	Buffer pH 7.0 ^a
4 <i>H</i> -Pyran-4-one (1)	—	—1.70
4 <i>H</i> -Thiopyran-4-one (3)	—1.01	—1.41
4 <i>H</i> -Pyran-4-thione (4)	—0.93	—1.33
4 <i>H</i> -Thiopyran-4-thione (5)	—0.72	—1.07
2 <i>H</i> -Thiopyran-2-thione (8)	—0.71	—1.12

^a 0.2 *M* citric acid, 0.2 *M* Na₂HPO₄.

energies, but an approximately linear relation exists between the energies of the maxima of the first bands in the electron spectra and the half-wave potentials. Finally, the half-wave potentials of five investigated pyrones are linear functions of the pH value of the medium in the range from pH 2 to pH 8.⁹⁰

⁹⁰ C. Párkányi and R. Zahradník, *Collection Czech. Chem. Commun.* **27**, 1355 (1962).

⁹¹ H. Adkins and F. W. Cox, *J. Am. Chem. Soc.* **60**, 1151 (1938).

⁹² L. Stárka and L. Jirousek, *Pharmazie* **14**, 473 (1959).

3. *Heats of Combustion and Aromaticity*

The values of the heats of combustion for 2,6-diphenyl- γ -thiapyrone and 2,6-diphenylthiapyran⁹³ were utilized for estimating⁸⁰ the "energy of aromatization" of thiapyrone as 32.7 kcal/mole. The values of the theoretical delocalization energies are sensitive to the choice of resonance integral for the C—X bond (2), and, therefore, the theoretical *DE* values must be judged very cautiously. If we base the estimate of the "aromaticity" on the simultaneous consideration of the values of the specific delocalization energies and of the extreme values of chemical reactivity indices,^{95, 94} the α - as well as the γ -pyrones appear as "not very aromatic systems."

4. *Dipole Moments*

The dipole moments of several γ -pyrones, particularly their methyl and phenyl derivatives, and of the corresponding sulfones, have been investigated.^{59, 80, 95-99} The two most recent papers are concerned with comprehensive groups of substances^{59, 99} (Table XI). All γ -pyrones are characterized by the high values of their dipole moments, which is obviously connected with the tendency to form an electron sextet in the ring; the negative charge is localized on the exocyclic atom. It is known¹⁰⁰ that the HMO method leads to excessively high values of the π electron component of the dipole moments (Table XII). From a simple consideration it is evident that, even in the case where the σ component of the dipole moment¹⁰¹ acts against the π electron component (as is the case, e.g., with γ -thiopyrone), no considerable influence is exerted upon the calculated high value of the π component. Although the HMO characteristics for the first excited state ($N \rightarrow V_1$) must be judged very cautiously, the $N \rightarrow V_1$ excitation is evidently accompanied by an intramolecular charge-transfer from the exocyclic atom and thus by a significant drop in the dipole moment (Table VI).

⁹³ L. Lorenz and H. Sternitzke, *Z. Elektrochem.* **40**, 501 (1934).

⁹⁴ R. Zahradník, unpublished material, 1963.

⁹⁵ E. C. E. Hunter and J. R. Partington, *J. Chem. Soc.* p. 87 (1933).

⁹⁶ G. Ran, *Proc. Indian Acad. Sci.* **A4**, 687 (1936).

⁹⁷ *Acta Physicochim. URSS* **6**, 639 (1937).

⁹⁸ G. C. Le Fèvre and R. J. W. Le Fèvre, *J. Chem. Soc.* p. 1088 (1937).

⁹⁹ M. Rolla, M. Sanesi, and G. Traverso, *Ann. Chim. (Rome)* **42**, 673 (1952).

¹⁰⁰ G. W. Wheland and D. E. Mann, *J. Chem. Phys.* **17**, 264 (1949).

¹⁰¹ R. Daudel, R. Lefebvre, and C. Moser, "Quantum Chemistry," p. 206. Wiley (Interscience), New York, 1959.

TABLE XI
DIPOLE MOMENTS OF 4*H*-PYRAN-4-ONES^a

Parent skeleton	Position of substituent		(D)
	2	6	
4 <i>H</i> -Pyran-4-one (1)	—	—	3.73
	CH ₃	CH ₃	4.58
	Ph	Ph	4.74
	CH ₃	Ph	4.61
	Ph	—	4.28
4 <i>H</i> -Thiopyran-4-one (3)	—	—	3.96
	CH ₃	CH ₃	4.30
	Ph	Ph	4.40
4 <i>H</i> -Pyran-4-thione (4)	—	—	4.08
	CH ₃	CH ₃	5.12
	Ph	Ph	5.31
	CH ₃	Ph	5.22
	Ph	—	4.79
4 <i>H</i> -Thiopyran-4-thione (5)	—	—	4.41
	CH ₃	CH ₃	4.90
	Ph	Ph	4.95

^a Reprinted by permission from Ref. 59.

TABLE XII
(HMO) π ELECTRON CONTRIBUTIONS^a TO DIPOLE MOMENTS (IN D)⁸⁴

Compound	μ_{π}	μ_{π}^*
4 <i>H</i> -Pyran-4-one (1)	11.6	5.3
4 <i>H</i> -Thiopyran-4-one (3)	12.1	7.5
4 <i>H</i> -Pyran-4-thione (4)	10.0	3.4
4 <i>H</i> -Thiopyran-4-thione (5)	10.5	4.7

^a μ_{π} (μ_{π}^*) is the dipole moment in the basic (excited) state. Parameters: 1.

5. Radio-Frequency Spectroscopy

a. *Nuclear Magnetic Resonance (NMR)*. The NMR spectra of γ -thiapyrone, γ -thiopyrone, and γ -thiathiopyrone (but not γ -pyrone) were completely analyzed as type A₂B₂.¹⁰² The appearance of the spectra

¹⁰² J. Jonáš, W. Derbyshire, and H. S. Gutowsky, *J. Phys. Chem.* **69**, 1 (1965).

of the individual substances is similar, except that the chemical shift between the A and B protons decreases in passing from γ -pyrone to γ -thiathiopyrone. Chemical shifts and coupling constants are summarized in Table XIII. The designation of protons and coupling constants is given in Fig. 8. Analyses of the spectra were carried out

TABLE XIII
NMR CHARACTERISTICS OF 4H-PYRAN-4-ONES^{a,b}

Compound	ν_A	ν_B	$\Delta\nu$	J_A	J_B	J	J'
4H-Pyran-4-one (1)	482.6	389.3	93.3	2.8 ₉	1.2 ₂	6.3 ₃	0.4 ₂
4H-Thiopyran-4-one (3)	469.5	415.7	53.8	4.1 ₂	2.0 ₀	10.7 ₄	0.4 ₄
4H-Pyran-4-thione (4)	448.6	421.9	26.7	2.2 ₀	0.8 ₈	5.7 ₉	0.6 ₅
4H-Thiopyran-4-thione (5)	471.8	452.5	19.3	3.4 ₁	1.7 ₉	10.3 ₉	0.6 ₇

^a Reprinted by permission from Ref. 102.

^b The chemical shifts are in cps downfield from tetramethylsilane at 60 Mc/sec.

for all combinations of the signs of the coupling constants.¹⁰³ With the possible exception of γ -pyrone, all coupling constants are positive. The spectrum of γ -pyrone is of the A_2X_2 type and thus does not allow determination of the relative signs of the coupling constants. The downfield shift of the midpoint of the spectra which is caused by the introduction of sulfur is interpreted in terms of an increased ring

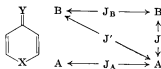


FIG. 8. Designation of protons and coupling constants in pyrones.¹⁰²

current.¹⁰² The NMR spectra of methyl derivatives of γ -pyrone have been examined in connection with the study of exchange reactions.¹⁰⁴

b. *Electron Spin Resonance (ESR)*. The ESR spectra of radical anions and radical cations of type 45 have not yet been investigated. The radical anion could probably be formed by electroreduction in an aprotic medium, and a radical cation in sulfuric acid in the presence of air. Figure 9 presents the values of the squares of the expansion co-

¹⁰³ J. D. Swalen and C. A. Reilly, *J. Chem. Phys.* **37**, 21 (1962).

¹⁰⁴ D. W. Mayo, P. J. Sapienza, and W. D. Phillips, *J. Org. Chem.* **29**, 2682 (1964).

efficients of the frontier orbitals (HOMO, LFMO), permitting the estimation of the values of the hyperfine splitting constants.¹⁰⁵ The signal for the radical anion will be split by interaction of the unpaired electron with the 2,6 protons, while in the radical cation

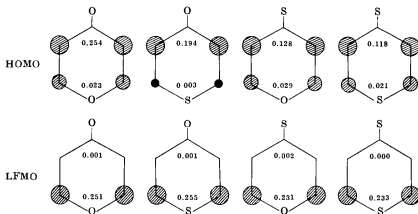
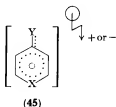


Fig. 9. Values of the squares of the expansion coefficients in the highest occupied (HOMO) and the lowest unoccupied (LFMO) molecular orbital. For clarity, these values are also indicated by circles with radii equaling the pertinent coefficient (Parameters 1).

interaction with 3,5 protons will dominate (cf. Fig. 9). The lines of the anion triplet will probably be further split by interaction (small hfs constant) with the second pair of protons, since the occurrence of negative spin densities must be considered.¹⁰⁵



C. CHEMICAL REACTIVITY

The chemical reactivity is usually discussed in terms of static (π electron densities, free valences) and dynamic (localization energies,

¹⁰⁵ A. Carrington, *Quart. Rev. (London)* **17**, 67 (1963).

superdelocalizabilities) indices.¹⁰⁶ Figures 10 and 11 present the molecular diagrams of α - and γ -pyrones.⁹⁴ The calculations were

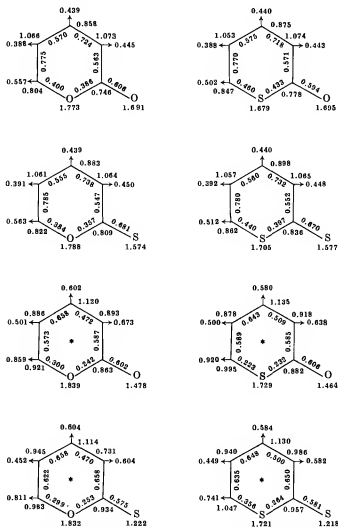


FIG. 10. Molecular diagrams of 2H-pyran-2-ones (Parameters 4) in the ground state and in the $N \rightarrow V_1$ excited state (*).

¹⁰⁶ R. D. Brown, *Quart. Rev. (London)* **6**, 63 (1952).

carried out for the following values of empirical parameters [for a definition of the quantities see Eqs. (7) and (8)].⁶⁵

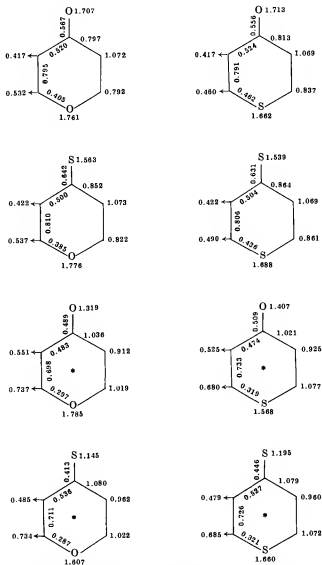


FIG. 11. Molecular diagrams of 4H-pyran-4-ones (Parameters 4) in the ground state and in the $N \rightarrow V_1$ excited state (*).

Parameters 4

Endocyclic atoms	Exocyclic atoms
$\delta_a = 1$	$\delta_b = 0.5$
$\rho_{cs} = 0.6$	$\rho_{cs} = 0.9$
$\delta_o = 2$	$\delta_o = 1$
$\rho_{co} = 0.8$	$\rho_{co} = 1$

The molecular diagrams for a different set of parameters are given in Ref. 72; see also Ref. 66.

From the data in Figs. 10 and 11 and from the values of the localization energies⁷² and superdelocalizabilities it is apparent that all indices lead to the same order of the reactivity centers, so that the "noncrossing rule"¹⁰⁶ is satisfied. The theoretical prediction of the reactivity centers is presented in Fig. 12. This holds over a wide range

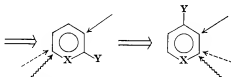


FIG. 12. Theoretically expected reactivity centers of α - and γ -pyrones. X and Y denote N, O, or S; \downarrow , \downarrow , \downarrow denote the centers of electrophilic, nucleophilic, and radical reactivity, respectively; \downarrow indicates bond of highest order.

of parameter values. The molecular diagrams of the excited state indicate that the $N \rightarrow V_1$ excitation changes the positions of reactivity. Moreover, although the experimental and theoretical values of the dipole moments point to a significant contribution from structures 3a-5a and 3b-5b, the bond orders of the C—C double bonds of the Kekulé structure of type A are obviously high. Accordingly, substitution reactions of γ -pyrones do not proceed very readily. A survey of the substitution reactions of γ -pyrones has been published,⁹⁰ and the theoretical predictions are in agreement with experiment. The theoretical reactivity centers of benzo- α -pyrones and benzo- γ -pyrones are shown in Fig. 13.

Although numerous thiopyrones have been synthesized, systematic investigations of their reactivities have not yet been made, and so reliable quantitative data, for a comprehensive correlation with the

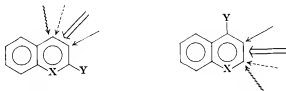


FIG. 13. Theoretically expected reactivity centers of benzo- α - and γ -pyrones.⁹⁴ For designation see Fig. 12.

present theoretical calculations, are not available. In the following section we give an account of some characteristic reactions.

1. Formation of Salts and Alkylation at the Thiocarbonyl and Carbonyl Group

Both the thiocarbonyl and the carbonyl compounds are such weak bases that they give no measurable basic reactions in dilute aqueous media. Therefore the conventional titration methods for the determination of basicity constants fail in these cases. If the base and its conjugate acid show different spectral absorptions, the basicity constants can be determined spectrophotometrically in concentrated acid solutions (see Ref. 88).

The pK value has so far been determined only for the protonation of 2*H*-thiopyran-2-thione.⁸⁸ The protonation takes place on the exocyclic atom, giving a structure resembling a derivative of the pyrylium ($X=O$) or thiopyrylium ($X=S$) ion. Comparative measurements have also been carried out for trithione (Table XIV). It is evident that

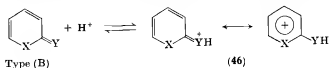


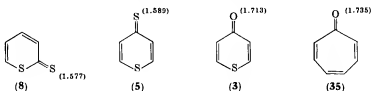
TABLE XIV
DISSOCIATION CONSTANTS⁸⁸

Compound	λ_{\max} (B) ^a	λ_{\max} (BH ⁺) ^a	pK_a ^b
2 <i>H</i> -Thiopyran-2-thione (8)	426	374	-3.21
1,2-Dithiol-3-thione (18)	398	348	-3.94

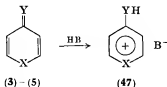
^a Wavelength in $m\mu$.

^b Measured in H_2SO_4 .

2*H*-thiopyran-2-thione, which is more basic than trithione, exhibits a higher π electron density on the exocyclic sulfur. It would be more correct, of course, to compare the difference in the π electron energies of the protonated and the nonprotonated forms. However, for conjugated systems these quantities are interrelated,¹⁰⁷ and it is consequently possible to estimate the order of basicity of structurally related compounds by means of the π electron densities. The expected order of increasing basicity of the following four substances is (the π electron densities are given in parentheses):

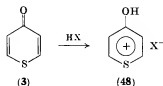


Since $N \rightarrow V_1$ excitation shifts the electrons from the exocyclic atom into the nucleus, the pK_a values of the excited state will be more negative. In their preparative separation and isolation the solubility of thiopyrones in relatively concentrated acids is often used, as the thiopyrones reprecipitate on dilution with water. However, in our experience considerable decomposition often occurs under these conditions. The driving force in forming the salt arises from the emergence of the pyrylium system (47).

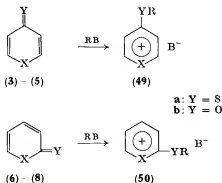


Attempts to substitute the nucleus of 4*H*-thiopyran-4-one (3) are of interest: whereas bromine reacts on γ -pyrone (1), to give 3-mono-substituted and 3,5-disubstituted bromopyrones, no bromination of the nucleus occurs with 4*H*-thiopyran-4-one (3) under a variety of conditions.⁶⁰ An unstable complex is formed, from which 3 may be regenerated (but see Ref. 90). On nitration of 3 only the pyrylium salt (48, $X = NO_3$) is obtained.⁹⁰ The corresponding hydrochloride (48, $X = Cl$) is also stable and can be sublimed.⁹

¹⁰⁷ S. Guha and R. Zahradník, unpublished material, 1964.



Under acidic conditions, **3** is evidently deactivated towards electrophilic attack by salt formation. The deduction⁵⁰ from this of an insignificant degree of "aromaticity" of **3** appears unjustified as the same authors find in the NMR spectra (in deuterochloroform) chemical shifts (τ values) of 2.11 and 2.91, characteristic of aromatic systems. For the characteristic color reactions on complexing, see Refs. 28, 32, 56, and 108. The high electron density at the sulfur atom of pyranthiones provides an explanation for the fact that electrophilic attack of alkylating agents occurs preferentially at the thiocarbonyl sulfur, forming alkylmercaptopyrylium salts (**49a** and **50a**).



On quaternization the original carbonyl or thiocarbonyl group becomes considerably more reactive, a property which is frequently used in preparative practice. The anion may be exchanged; this becomes important when well-crystalline salts are required, particularly in the case of the perchlorates, and quite recently the nonexplosive perrhenates. A range of alkylating agents may be employed; the reaction has been extensively investigated, particularly in the 4*H* series.^{109, 110} Thus, 2,6-dimethylpyran-4-thione and the parent

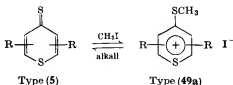
¹⁰⁸ M. A.-F. Elkashef and M. H. Nosseir, *Egypt J. Chem.* **2**, 355 (1959).

¹⁰⁹ L. C. King, F. J. Ozog, and J. Moffat, *J. Am. Chem. Soc.* **73**, 300 (1951).

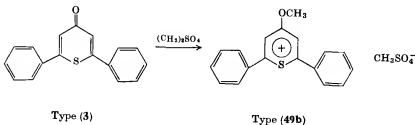
¹¹⁰ F. J. Ozog, V. Comte, and L. C. King, *J. Am. Chem. Soc.* **74**, 6225 (1952).

compound (4) are easily methylated, both by methyl iodide and dimethyl sulfate²¹ (49a, X = CH₃SO₄⁻).

The use of alkyl bromides and chlorides, chloroacetone, and chloromethyl ether mostly yields oily products in slow reactions. With phenacyl bromide the rate of the reaction depends on the kind and on the position of the substituents in the phenacyl bromide.¹¹⁰ -I substituents favor the reaction. As a rule the initial thio compounds are readily regenerated from *S*-alkylthiopyrylium salts (49a and 50a) by bases. We already referred to this while discussing the synthesis of thiopyrones.



In principle, alkylation and thus formation of pyrylium salts proceed easier with thiopyrones containing a thiocarbonyl group than with those containing a carbonyl group. In the last-mentioned cases *O*-methylation is possible, however, as in the *O*-methylation of 2,6-diphenylthiopyran-4-one with dimethyl sulfate.³¹ The product can be made to crystallize as the perchlorate.



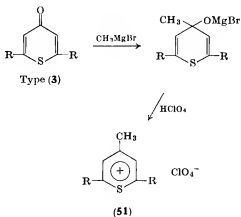
By the action of mercaptans on 4-methoxythiopyrylium salts of this kind the above-mentioned 4-*S*-alkylthiopyrylium salts of type 49a¹¹¹ are formed which can be used for many subsequent reactions (see Ref. 112).

On the action of diazomethane as "alkylating agent" on 2,6-diarylthiopyran-4-thione, and on the analogous action of diphenyl-

¹¹¹ R. Wizinger and P. Ulrich, *Helv. Chim. Acta* **39**, 217 (1956).

¹¹² R. Wizinger and P. Ulrich, *Helv. Chim. Acta* **39**, 207 (1956).

diazomethane and 9-diazofluorene, see Refs. 32 and 56, and the following section.



2. Formation of Dipyrlylenes

Compounds with the thioketone structure frequently dimerize with elimination of sulfur (Eq. 11). In the thiopyrone series this was first

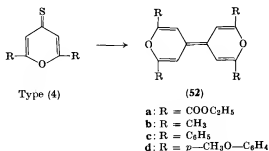


observed on heating the ester (4a),^{20, 28} which at room temperature is converted slowly into a derivative of 4,4'-bis-4*H*-pyran, the dipyrlylene (52).

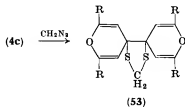
The mechanism of formation of 52 is still not clear. As with the parent compound 4 (R = H), and the 2,6-dimethyl derivative (4b), no dimerization on desulfurization has been observed; undoubtedly the nature of the substituent is of decisive importance in the formation of dipyrlylene. As a working rule it can be assumed that dipyrlylenes are very easily formed from thiopyrones if the thioketone nature of the thione group is well-developed, for instance if it reacts with carbonyl reagents. This is particularly the case with -I substituents. According to the principle of vinylogy¹¹³ special differences also are to be explained; thus the 2,6-diphenyl-4*H*-pyran-4-thione (4c), the vinylog of the thermolabile thiobenzophenone, yields the dipyrlylene (52c) on melting in an inert atmosphere,²⁰ but 4d, corresponding to the thermostable 4,4'-dimethoxythiobenzophenone, is recovered

¹¹³ A. Schönberg, M. M. Sidky, and G. Aziz, *J. Am. Chem. Soc.* **76**, 5115 (1954).

unchanged under the same reaction conditions.⁵⁶ In the latter case reaction occurs only on heating with copper powder in xylene.^{56, 60}



Dipyrlylenes of type 52 are also formed by the action of organometallic compounds upon thiopyrones of type 4. Thus 4c is converted into 52c by phenyllithium or by phenylmagnesium bromide.^{56, 114} Dipyrlylenes are also formed on treatment of 4 with diazo compounds. The nature of the substituents is of importance here too. The 2,6-di-(*p*-methoxyphenyl)-4*H*-pyran-4-thione (4d) immediately yields the dipyrlylene (52d) with diazomethane,⁵⁶ but 2,6-diphenyl-4*H*-pyran-4-thione (4c) forms the 1,3-dithiolane (53)³² by analogy with the 4-thioflavone.^{115, 116}

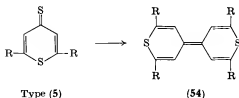


In contrast to the γ -thiopyrone (4c), the corresponding α -thiopyrone of type 7 is unchanged on heating, and does not yield a dipyrlylene-like product.⁴¹ Nor does it form an oxime.⁴¹ In these reactions the compound of the α series again proves to be less reactive than that of the γ series. Dithiopyrones (5) split off sulfur more readily than the monothiopyrones (4) and are converted into dithiopyrlylenes (54).¹¹⁶

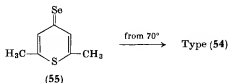
¹¹⁴ A. Schönberg, A. Rosenbach, and O. Schütz, *Ann.* **454**, 37 (1927).

¹¹⁵ A. Schönberg and S. Nickel, *Ber.* **64**, 2323 (1931).

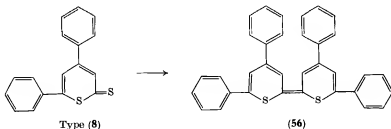
¹¹⁶ F. Arndt, P. Nachtwey, and J. Pusch, *Ber.* **58**, 1644 (1925).



In the case of selenones (55) the splitting off of selenium proceeds analogously and at lower temperatures, as might be expected.³¹



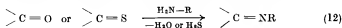
In the α -dithio series (8) desulfuration to 56 is possible too. In this case addition of copper powder is necessary.³⁴



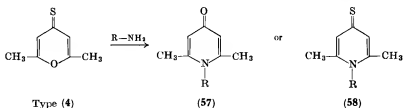
As a rule dipyrlylenes are characterized by chemical and thermal stability, but under special conditions cleavage of the ethylene bond can be achieved. Thus, on heating with thionyl chloride followed by treatment with water, the tetraphenyl derivative (52c) is converted into 2,6-diphenyl-4*H*-pyran-4-one.^{56,108} Only decomposition products were isolated with the corresponding methoxyphenyl derivative (52d).

3. Nucleophilic Attack by Amines

The more pronounced the double-bond character of the carbonyl or thiocarbonyl group, the easier is attack by amines acting by condensation as carbonyl reagents (Eq. 12). Thus, in contrast to most



thiopyrones, semicarbazones, oximes, and hydrazones of γ -pyrones and α -pyrones are not formed directly. It is a general rule that γ -thiopyrones (type A) react more easily than α -thiopyrones (type B). γ -Dithiopyrones of type 5 mostly react with amines at the thiocarbonyl group. This proceeds with particular ease if substituents increase the thione character, i.e., if they counteract the formation of the zwitterionic structure.^{13,116} This ease of reaction ordinarily runs parallel with the facilitated dimerization with loss of sulfur to form dipyrlylene (54). The influence of substituents on the thiocarbonyl group may be demonstrated in the 4*H*-pyran-4-thione series (4). These derivatives mostly behave like pronounced thiocarbonyl compounds, i.e., they readily form dipyrlylenes, and react with hydroxylamine to form oximes, and with semicarbazide to form semicarbazones.^{20, 25, 31, 56} But as soon as the thiocarbonyl character is disturbed by appropriate substituents and the zwitterionic nature becomes more pronounced, they become more thermostable and no longer form dipyrlylenes. Primary amines then do not react specifically at the thiocarbonyl group, but may instead produce structural changes elsewhere.^{25, 26}



The pyridone (57, R=OH) also results from 2,6-dimethyl-4*H*-pyran-4-thione with hydroxylamine.¹¹⁷

Substitution of the ring oxygen in 4 by nitrogen also succeeds with ammonia¹¹⁸ and primary alkyl or aryl amines,¹¹⁹⁻¹²² and yields 57 (R=H, alkyl, or aryl), or more frequently 1-alkyl-4-thiopyridones (58), which are also accessible from the analogous 57 by the action of phosphorus pentasulfide.

¹¹⁷ G. Soliman and I. El-Sayed El-Kholy, *J. Chem. Soc.* p. 1755 (1954).

¹¹⁸ R. M. Anker and A. H. Cook, *J. Chem. Soc.* p. 117 (1946).

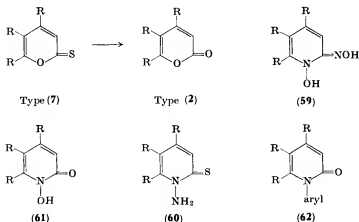
¹¹⁹ M. A.-F. Elkaschef and M. H. Nosseir, *J. Am. Chem. Soc.* **82**, 4344 (1960).

¹²⁰ M. Konrad and M. Guthzeit, *Ber.* **20**, 154 (1887).

¹²¹ W. Borsche and J. Bonacker, *Ber.* **54**, 2678 (1921).

¹²² M. A.-F. Elkaschef, M. H. Nosseir, and A. Abdel-Kader, *J. Chem. Soc.* p. 4647 (1963).

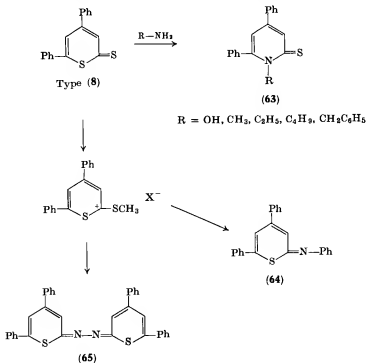
It is interesting to compare γ -pyrones (**1**) with 4*H*-thiopyran-4-one (**3**): although 4*H*-thiopyran-4-ones (**3**) are easily formed from the corresponding γ -pyrones (**1**) with KSH,^{5,50} they are by no means generally more stable than the γ -pyrones. In both cases the carbonyl group is only of limited reactivity and scarcely accessible to condensation reactions with nucleophilic reagents. With **3**, as with **1**, the action of hydrazine or hydroxylamine results in ring-opening and incorporation of nitrogen (leading to type **57**). Only from the parent compound (**3**) has the semicarbazone,⁸ and recently the 2,4-dinitrophenylhydrazine,⁵⁰ been obtained; the oxime¹⁰⁹ and the hydrazone are accessible only by other synthetic routes. No analogous reactions of γ -pyrone are known; the carbonyl activity of γ -pyrone is thus less than that of thiopyrone (**3**). A participation of the zwitterionic structure in the thiopyrone (**3**) is apparent from the position of the carbonyl band in the infrared spectra (**1**, $\nu_{C=O}$ 1658 cm^{-1} ; **3**, $\nu_{C=O}$ 1609 cm^{-1}). Some special features must be mentioned in the α -thiopyrone series **6–8**. Definite carbonyl reactions are rarely obtained with the 2*H*-pyran-2-thiones (**7**). Frequently, on reaction with hydrazine or hydroxylamine (but not with semicarbazide), the thiocarbonyl sulfur in **7** is replaced by oxygen,³⁰ but under suitable conditions hydroxylamine produces



the 1-hydroxypyridone-2-oxime (**59**), and hydrazine the 1-aminopyrid-2-thione (**60**). On the tautomerism of **61** see Ref. 30.

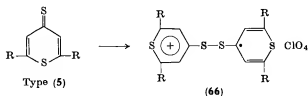
Occasionally the pyridone (**62**) has been observed by the action of primary aromatic amines upon 2*H*-pyran-2-thiones (**7**).⁴⁰ Of the α -dithiopyrones (**8**), so far only the 4,6-diphenyl derivative has been

thoroughly investigated.³⁴ It reacts with a wide variety of amines forming pyrid-2-thiones (63). Via the *S*-alkylthiopyrylium salts, the anil (64) is formed with aniline, and the azine (65) with hydrazine.³⁴

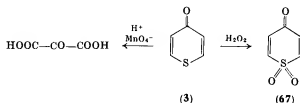


4. The Action of Oxidizing and Reducing Agents on Thiopyrones

Generally, thiopyrones are unstable towards oxidizing agents. As already mentioned (Section III, C; see also in tables), pyranthiones (types 4, 5, 7, 8) can be oxidized to the carbonyl compounds ($C=S \rightarrow C=O$). With some thiopyrones of type 5, meriquinoid salts (66) may be formed instead.

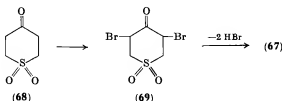


Thiopyrones containing ring sulfur and a carbonyl group (types 3 and 6) are attacked at the ring sulfur atom. The 4*H*-thiopyran-4-one system (3) has been investigated in detail. The parent compound (3) is oxidized by alkaline potassium permanganate, forming mesoxalic acid.^{8, 123} Hydrogen peroxide^{2, 6, 33} below 0° produces 4*H*-thiopyran-



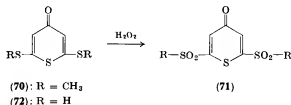
4-one-1,1-dioxide (67)³³ in small yield, but at higher temperatures only sulfuric acid was observed.²

The sulfone (67) is easily accessible, following a generally applicable procedure^{24, 116} starting from 68, via 69,^{2, 4, 124} and it has therefore been thoroughly investigated.¹²⁴ It behaves like an α, β -unsaturated ketone,^{13, 124} forming a semicarbazone and an oxime and giving



addition reactions at one or both double bonds. It is also reported¹²⁴ that with bromine in glacial acetic acid substitution occurs in the 3- and 5-positions.

On the IR spectra see Ref. 9.



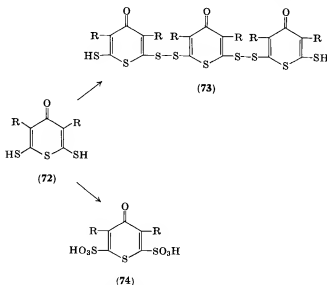
¹²³ W. S. Jegorowa, *Zh. Obshch. Khim.* **30**, 107 (1960); see also Ref. 8.

¹²⁴ E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.* **70**, 1813 (1948).

Differences in the reactivity of the ring and side chain sulfur atoms are evident in the oxidation of compound **70**.² In this case only the side chain sulfur is oxidized, forming the sulfone (**71**).

The thioesters (**70**) are available both by action of alkyl halides upon the corresponding dithiols (**72**), and by alkylation with diazo compounds.¹⁸ They are not attacked by hot dilute sodium hydroxide, but dissolved in hot acids giving yellow solutions from which they are precipitated unchanged on dilution with water. On the reactivity see Refs. 14, 15, 17, and 125.

The free mercapto compounds (**72**) are extremely stable towards alkalis and acids, but they are quickly attacked by oxidizing agents.^{15, 126} Disulfides (**73**) or disulfonic acids (**74**) are obtained, depending upon the conditions. On melting with alkali the latter compounds do not yield 2,6-dihydroxy derivatives but cleavage products.



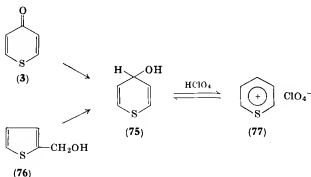
The behavior of the thiopyrones towards oxidizing agents explains why hydroxythiopyrones (pseudotropolones) are not accessible by direct oxidation.⁵³

Little is known of the reduction of thiopyrones. The parent compound (**3**) has been reduced to the 4*H*-thiopyran-4-ol (**75**) by aluminum

¹²⁵ H. Apitzsch, *Ber.* **41**, 4047 (1908).

¹²⁶ H. Apitzsch and G. A. Bauer, *Ber.* **41**, 4039 (1908).

hydride.¹²⁷ The alcohol (75) is also accessible by isomerization of the thiophene derivative (76).⁸ It gives (reversibly) the thiopyrylium ion (77) with perchloric acid. This reaction is analogous to the formation of the propylium cation from troyl alcohol. An estimate of the pseudobasicity can be made from the nucleophilic localization energies of the individual positions of the cation; these quantities, with neglect of hyperconjugation, are equivalent to the difference in the π electron energy of the pseudobase and of the corresponding cation. For irreversible reductions see Ref. 13.



5. General Aspects

As can be seen from the foregoing, it does not seem possible, in the light of present knowledge, to make valid generalizations concerning the reactivity of the individual thiopyrones, their "aromatic character," or other properties. In special cases reactivity and stability suggest a certain "aromatic" behavior of thiopyrones (see Ref. 128), but other facts seem to contradict this. It is debatable whether one can deduce from the physical data an important contribution from the zwitterionic state and a pronounced aromaticity from the salt like character which is a result of this.

In part, however, considerable variations occur in the behavior as pointed out in the literature (e.g., Ref. 2). Thus 4*H*-thiopyran-4-one (3) melts higher, crystallizes better, and dissolves to a lower degree in organic solvents but better in water than γ -pyrone (1). However, for reactivity see Ref. 50.

¹²⁷ I. Degani, R. Fochi, and C. Vincenzi, *Tetrahedron Letters* p. 1167 (1963).

¹²⁸ A. R. Katritzky and R. A. Jones, *Spectrochim. Acta* **17**, 64 (1961).

As to the chemical reactions in the α -dithiopyrone series (8), the parallel with the 1,2-dithiol-3-thiones (trithiones) (18 and type 37) already noticed with the parent compounds (8 and 18)³⁸ is extensive. We have compared 4,6-diphenyl- α -dithiopyrone and 5-phenyl-1,2-dithiol-3-thione and established the complete analogy of these two systems with regard to their reactivity.^{34,129} Methyl-substituted thiopyrones or thiopyrones containing methylene groups mostly are less stable than the aryl-substituted compounds and are frequently susceptible to condensations (e.g., with aldehydes) at the methyl or methylene group (see Ref. 130). The thiopyrylium salts are even more reactive in this way. These results are analogous to those found with trithiones and 1,2-dithiolium salts containing active methyl and methylene groups, which recently have been extensively investigated.¹³¹

ACKNOWLEDGMENT

We thank Dr. Mechthild Fischer for the assistance she gave in translating and correcting this report.

¹²⁹ R. Mayer and H. Spiess, unpublished material, 1965.

¹³⁰ M. A.-F. Elkaschef, M. H. Nosseir, and A. Abdel-Kader, *J. Chem. Soc.* p. 440 (1963).

¹³¹ R. Mayer and H. Hartmann, *Ber.* **97**, 1886 (1964); H. Hartmann and R. Mayer, *Z. Chem.* **5**, 152 (1965).

Indoxazenes and Anthranils

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I. Introduction

Two series of benzo derivatives are derived from isoxazole. They have both been known for over 50 years, and have been the subject of many investigations.

Each ring system is known in the literature by several names. Thus, **1** is described as indoxazene, 1,2-, 4,5-, or α,β -benzisoxazole, benz[*d*]isoxazole, or simply benzisoxazole, while for **2** the names anthranil, anthroxan, 2,1-, 3,4-, and $\beta\gamma$ -benzisoxazole, benz[*c*]isoxazole, and benzpseudoxazole can be found. The preferred nomenclature of *Chemical Abstracts* and the *Ring Index* is 1,2-benzisoxazole for **1** and

2,1-benzisoxazole for **2**, but for the most part, in the interest of clarity and brevity, we shall use the common names indoxazene and anthranil in this chapter.



(1)



(2)

There has hitherto been no systematic coverage of either ring system, the most extensive review to date being that by Quilico in the Interscience series of monographs on "The Chemistry of Heterocyclic Compounds".¹ Otherwise, only brief sections in the larger textbooks deal with these compounds.²⁻⁴ More highly condensed systems, and also hydrogenated benzisoxazoles, will be discussed here, besides the basic systems themselves.

This article covers material appearing in *Chemical Abstracts* and *Chemisches Zentralblatt* to the middle of 1965; original sources have been consulted where possible. A certain amount of more recent work is also included.

II. 1,2-Benzisoxazoles (Indoxazenes)

A. FORMATION

The most generally applicable methods of synthesis of indoxazenes fall into two main classes:

- (1) cyclization of oximes of aryl ketones, forming bond 1—7a, with elimination of a substituent from the aromatic ring (3)—the oxime may be prepared *in situ* (4);
- (2) formation of bond 1—2, eliminating a group from the nitrogen atom (5), or inserting the nitrogen atom by suitable means, and forming bonds 1—2 and 2—3 (6).

¹ A. Quilico, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 17, pp. 159–176. Wiley (Interscience), New York, 1962.

² J. D. Loudon, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. 4, pp. 348–353. Elsevier, Amsterdam, 1957.

³ P. Jullien, in "Traité de Chimie organique" (V. Grignard, ed.), Vol. 21, pp. 343–347. Masson, Paris, 1953.

⁴ A. A. Morton, "The Chemistry of Heterocyclic Compounds," pp. 425–427. McGraw-Hill, New York, 1946.



(3)



(4)



(5)

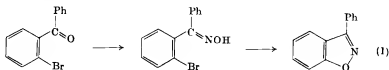


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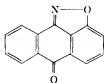
Other methods are of far less general use.

1. Closure of Bonds 1—7a, or 1—7a and 2—3

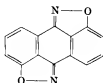
a. *From o-Halogenobenzoyl Compounds and Hydroxylamine.* In 1892 Cathcart and Meyer⁵ obtained 3-phenylindoxazene by the action of hydroxylamine on *o*-bromobenzophenone in an alkaline medium. In acid solution the reaction proceeds only as far as the oxime, but in alkali cyclization occurs [Eq. (1)]. The reaction has been extended to



substituted *o*-bromobenzophenones,⁶⁻¹⁰ *o*-bromophenyl naphthyl ketone,¹¹ and *o*-bromophenyl alkyl ketones.¹²⁻¹³ Chloroanthraquinones give condensed indoxazenes of types 7 and 8.¹⁴ Usually, the oxime is prepared first, and is subsequently cyclized with alkali. Chloro



(7)



(8)

⁵ W. R. Cathcart and V. Meyer, *Ber. Deut. Chem. Ges.* **25**, 1498 (1892).

⁶ A. Heidenreich, *Ber. Deut. Chem. Ges.* **27**, 1452 (1894).

⁷ J. Meisenheimer, P. Zimmermann, and K. von Kummer, *Ann. Chem.* **446**, 205 (1925).

⁸ J. Meisenheimer, R. Hanssen, and A. Wächterowitz, *J. Prakt. Chem.* [2] **119**, 315 (1928).

⁹ W. Borsche and W. Scriba, *Ann. Chem.* **540**, 83 (1939).

¹⁰ P. J. Montagne, *Rec. Trav. Chim.* **27**, 340 (1908).

¹¹ R. J. Knoll and P. Cohn, *Ber. Deut. Chem. Ges.* **28**, 1872 (1895).

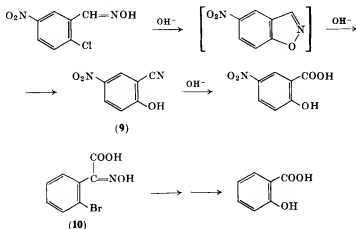
¹² W. Borsche and W. Scriba, *Ann. Chem.* **541**, 283 (1939).

¹³ W. Borsche and A. Herbert, *Ann. Chem.* **546**, 277 (1941).

¹⁴ M. Freund and F. Achenbach, *Ber. Deut. Chem. Ges.* **43**, 3251 (1910).

compounds react less readily than the bromo derivatives,^{7, 15, 16} iodo,^{15, 17, 18} and particularly also fluoro^{9, 19} derivatives, more readily.

3-Unsubstituted indoxazenes cannot be prepared in this way; instead of the expected product one obtains the corresponding isomeric salicylonitrile (9) or its hydrolysis products.²⁰ With *o*-bromophenylglyoxylic acid oxime (10) in alkaline solution the reaction proceeds similarly, with decarboxylation, ring opening, and hydrolysis to salicylic acid.²¹



The configuration of the oxime is important to the course of the reaction. Thus, while the β -oxime (11) gives the indoxazene or its degradation products, the α -oxime (12) undergoes a Beckmann rearrangement, finally yielding benzoxazole (13). This difference in reaction pathway between stereoisomeric oximes was used in the determination of their configurations.^{7, 8, 22, 23}

¹⁵ W. R. Cathcart and V. Meyer, *Ber. Deut. Chem. Ges.* **25**, 3291 (1892).

¹⁶ R. Fusco, G. Bianchetti, and G. Cignarella, *Ann. Chim. (Rome)* **46**, 122 (1956); *Chem. Abstr.* **50**, 13829 (1956).

¹⁷ W. Wachter, *Ber. Deut. Chem. Ges.* **26**, 1744 (1893).

¹⁸ C. Willgerodt and R. Gartner, *Ber. Deut. Chem. Ges.* **41**, 2813 (1908).

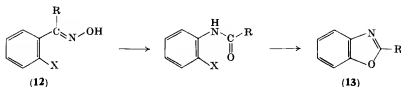
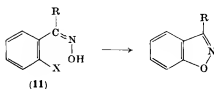
¹⁹ W. Borsche and M. Wagner-Roemmich, *Ann. Chem.* **546**, 273 (1941).

²⁰ V. Meyer, *Ber. Deut. Chem. Ges.* **26**, 1250 (1893).

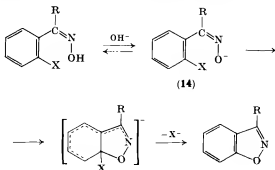
²¹ A. Russanow, *Ber. Deut. Chem. Ges.* **25**, 3297 (1892).

²² J. Meisenheimer and H. Meis, *Ber. Deut. Chem. Ges.* **57**, 289 (1924).

²³ O. L. Brady and G. Bishop, *J. Chem. Soc.* **127**, 1357 (1925).



The formation of the indoxazene from the oxime proceeds via the anion (14) of the latter; cyclization does not occur with pyridine as a base.⁹ The negatively charged oxygen atom attacks the *ortho* position of the benzene ring, and the halogen is eliminated as halide ion. The halogen atom undoubtedly receives some activation towards nucleophilic displacement, even when the ring contains no nitro groups, from the adjacent ketoxime grouping, while the proximity of the displacing group also assists the reaction. The cyclization has been shown by kinetic experiments to be the rate-determining step.²⁴

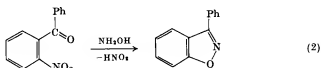


b. *From o-Nitrobenzoyl Compounds and Hydroxylamine.* *o*-Nitrobenzophenone and hydroxylamine give 3-phenylindoxazene²⁰ [Eq. (2)], but *o*-nitrophenylglyoxylic acid oxime²⁰ and *o*-nitrobenzil mono- and dioximes²⁵ form the salicylic acid or *o*-nitrobenzoic acid derivatives, while 1-nitroanthraquinone dioxime does not react at all.²⁵

²⁴ J. F. Bunnett and S. Y. Yih, *J. Am. Chem. Soc.* **83**, 3805 (1961).

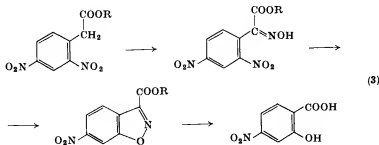
²⁵ O. List, *Ber. Deut. Chem. Ges.* **26**, 2451 (1893).

The oximes necessary for the cyclization can also be obtained from the corresponding *o*-nitrobenzyl compounds, by nitrosation with an



alkyl nitrite in the presence of sodium alkoxide,²⁶⁻³² or with nitrous acid.³⁸ The oximes are cyclized by alkali, although this reaction may not occur when the stereochemistry of the oxime is unfavorable³² [Eq. (3)].

This method has proved particularly useful for the preparation of methyl 6-nitroindoxazine-3-carboxylate,^{26, 27, 29, 30, 33} an intermediate in the synthesis of *p*-nitro- and *p*-aminosalicylic acid (Section II, C, 3, c), but 3-acyl²⁷ and 3-methyl²⁸ derivatives have been obtained similarly. In most of the published examples there is a second nitro group *meta* to the first in the benzene ring.



²⁶ W. Borsche, *Ber. Deut. Chem. Ges.* **42**, 1310 (1909).

²⁷ W. Borsche, *Ann. Chem.* **390**, 1 (1912).

²⁸ S. Reich and V. Nicolaeva, *Helv. Chim. Acta* **2**, 84 (1919).

²⁹ S. Hillers, A. Lokenbachs, and L. Majis, *Latvijas PSR Zinatnu Akad. Vestis* No. 3, 7 (1950); *Chem. Abstr.* **48**, 9964 (1954).

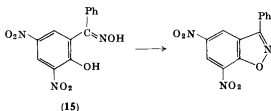
³⁰ S. S. Sabnis and M. V. Shirsat, *J. Sci. Ind. Res. (India)* **17B**, 451 (1958); *Chem. Abstr.* **53**, 11291 (1959).

³¹ S. Reich and V. Nikolaeva, *Bull. Soc. Chim. France* [4] **25**, 192 (1919).

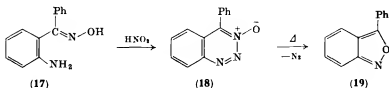
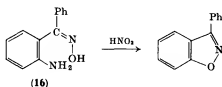
³² A. Kövendi and M. Kircz, *Chem. Ber.* **97**, 1902 (1964).

³³ T. Reetz (Nordmarkwerke G.m.b.H.), German Patent 800,666; *Chem. Abstr.* **45**, 1627 (1951).

c. *From Other o-Substituted Benzoyl Compounds and Hydroxylamine.* Salicylaldehyde itself does not give indoxazine directly.³⁴ In **15**, however, the hydroxy group is so activated by the two nitro groups that the compound is cyclized even in water.⁷ An activated methoxy group may also be displaced in the cyclization.⁷ The structure of a by-product from the reaction between 7-methylcoumarin and hydroxylamine, formulated as an indoxazine-3-acetic acid, arising via an *o*-hydroxybenzoyl acetic acid oxime,³⁵ is based on uncertain evidence (see Section IV).



o-Aminobenzophenone oxime gives 3-phenylindoxazine with nitrous acid.^{36, 37} The stereochemistry of the oxime is important here: with the hydroxy group oriented *syn* to the aminophenyl group (the "h-oxime," **16**) an almost quantitative yield of the indoxazine is obtained, while the *anti*-("n")-oxime (**17**) forms the benzotriazine oxide (**18**), which can be decomposed to form 3-phenylanthranil (**19**).³⁷



³⁴ H. Lindemann and H. Thiele, *Ann. Chem.* **449**, 63 (1926).

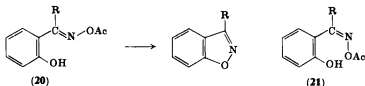
³⁵ T. Posner and R. Hess, *Ber. Deut. Chem. Ges.* **46**, 3816 (1913).

³⁶ F. von Meyenburg, *Ber. Deut. Chem. Ges.* **26**, 1657 (1893).

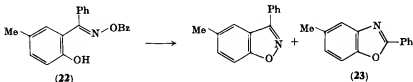
³⁷ J. Meisenheimer, O. Sonn, and P. Zimmermann, *Ber. Deut. Chem. Ges.* **60**, 1736 (1927).

2. Closure of Bonds 1—2, or 1—2 and 2—3

a. *From o-Hydroxybenzoyl Oxime Derivatives.* The thermal decomposition under reduced pressure of suitable *O*-acyloximes is a method of practical value for the preparation of indoxazenes. Salicylaldehyde *O*-acetyloxime (**20**, R = H) provides unsubstituted indoxazene by this method.³⁴ 3-Alkyl^{34, 38–40} and 3-aryl⁴¹ derivatives may similarly be obtained. Besides thermal decomposition, the calculated quantity of base has also been reported to effect cyclization.³⁸



Again, the configuration of the oxime is of significance. The acetate (**20**, R = Ph) provides the indoxazene smoothly on pyrolysis, while its isomer (**21**) gives only a small yield of the same product.⁴² A Beckmann rearrangement diverts the pyrolysis of some of the oxime benzoate (**22**) to the formation of the benzoxazole (**23**).⁴³



Salicylamidoxime cannot be dehydrated directly to an indoxazene; for example, with phosphorus pentoxide it rearranges to give 2-aminobenzoxazole.⁴³ However, its oxime-*O*-ethoxycarbonyl derivative (**24**) provides 3-aminindoxazene (**25**) on heating.⁴⁴

³⁸ H. Lindemann and W. Pickert, *Ann. Chem.* **456**, 275 (1927).

³⁹ H. Lindemann, H. Könitzer, and S. Romanoff, *Ann. Chem.* **456**, 284 (1927).

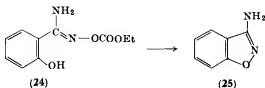
⁴⁰ H. Lindemann and S. Romanoff, *J. Prakt. Chem.* [2] **122**, 214 (1929).

⁴¹ D. A. Reich and D. V. Nightingale, *J. Org. Chem.* **21**, 825 (1956).

⁴² A. H. Blatt and L. A. Russell, *J. Am. Chem. Soc.* **58**, 1903 (1936).

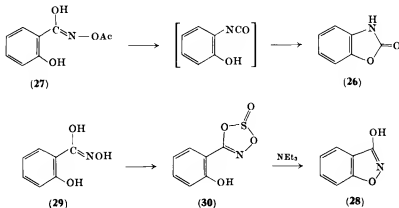
⁴³ A. H. Blatt, *J. Am. Chem. Soc.* **60**, 205 (1938).

⁴⁴ H. Böhagen and E. Schraufstätter, *Angew. Chem.* **72**, 1000 (1960); H. Böhagen (Farbenfabriken Bayer A.G.), German Patent 1,129,488; *Chem. Abstr.* **57**, 13760 (1962).



Sulfuric acid is reported to cyclize 2-benzoyl-1-naphthol oxime to the corresponding naphthoisoazole;⁴⁵ if this is correct, it may be an example of a 1,2 closure, via the oxime *O*-sulfonate.

The benzoxazolinone (26) is formed via a rearrangement, on heating the acetylhydroxamic acid (27)—preferably with alkali.⁴⁷ The compound which the same authors described as indoxazen-3-one was later⁴⁶ shown to be salicylamide.



A successful synthesis of 3-hydroxyindoxazene (28) starts from salicylhydroxamic acid (29), which gives a cyclic mixed anhydride (30) with thionyl chloride; 30 is converted into the indoxazene with triethylamine.⁴⁸

b. *Miscellaneous Reactions.* Although the mechanism of reaction, and the precise intermediates involved, in the earliest synthesis of

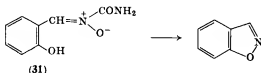
⁴⁵ O. Dischendorfer, H. Hinrichs, and J. Schewtschenko, *Monatsh. Chem.* **75**, 31 (1944).

⁴⁶ H. Lindemann and H. Cissée, *J. Prakt. Chem.* [2] **122**, 232 (1929).

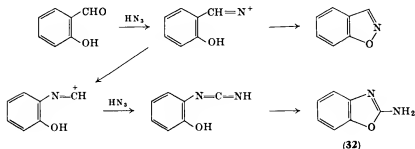
⁴⁷ H. Lindemann and W. Schultheis, *Ann. Chem.*, **451**, 241 (1927).

⁴⁸ H. Böshagen (Farbenfabriken Bayer A.G.), German Patent 1,157,231; *Chem. Abstr.* **60**, 5507 (1964).

indoxazene, by Conduché,⁴⁹ are not quite clear, it is probable that the preparation belongs to the group of cyclizations by 1—2 bond formation. Salicylaldehyde and hydroxyurea condense to give what may be the nitron (31) (originally⁴⁹ formulated as an oxaziridine), which is treated with the exact equivalent of alkali to provide indoxazene. A recent, and more convenient, synthesis of indoxazene is described in Section IV.



Substituted salicylaldehydes react with hydrazoic acid in sulfuric acid to give indoxazenes;^{50,51} up to 15% of the corresponding 2-aminobenzoxazole (32) may be obtained as a by-product. The reaction is a variant of the Schmidt reaction, in which the intermediate nitrenium ion may cyclize at once to the indoxazene, or rearrange and react with more hydrazoic acid, ultimately providing the benzoxazole.



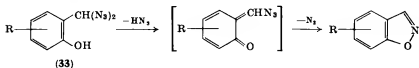
A related reaction occurs on pyrolysis of *o*-hydroxybenzal azides (33) which are readily obtained from the corresponding chlorides with potassium azide. By heating, in acetic acid or nitrobenzene, or without a solvent, they are converted into indoxazenes, possibly through inter-

⁴⁹ A. Conduché, *Ann. Chim. (Paris)* [8] **13**, 47 (1908).

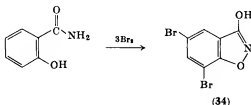
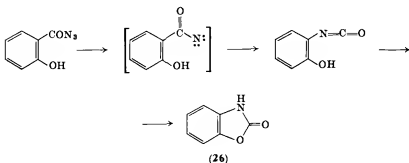
⁵⁰ S. Palazzo and B. Tornetta, *Boll. Sedute Accad. Gioenia Sci. Nat. Catania* **4**, 205 (1957–1958); *Chem. Abstr.* **53**, 338 (1959).

⁵¹ G. Caronna and S. Palazzo, *Gazz. Chim. Ital.* **89**, 1009 (1959).

mediate quinone methide derivatives. By-products were not found in this reaction.⁵²



The azide of salicylic acid does not provide the hydroxyindoxazene (indoxazen-3-one) on heating in benzene; instead, it gives the benzoxazolin-2-one (**26**) via a Curtius rearrangement.⁴⁷ A similar reaction has been reported with a hexahydrosalicylic acid azide.⁵³



Bromination of salicylamide has been reported to proceed with oxidative ring closure to give a dibromo-3-hydroxyindoxazene (**34**).⁵⁴ The structure of this product is very doubtful, however, since Böhshagen⁴⁸ has described the same compound with a much higher melting point.

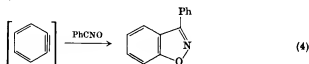
⁵² H. Lindemann and A. Mülhaus, *Ann. Chem.* **446**, 1 (1925).

⁵³ J. Sicher, F. Šipoš, and M. Tichý, *Collection Czech. Chem. Commun.* **26**, 847 (1961).

⁵⁴ H. Freiser and J. L. Walter, *J. Org. Chem.* **18**, 256 (1953).

3. Closure of Bonds 1—7a and 3—3a

Indoxazene derivatives are also accessible by 1,3-dipolar cycloaddition of nitrile oxides or nitrones to suitable dipolarophiles. Minisci and Quilico⁵⁵ obtained the 3-phenyl compound by addition of benzonitrile oxide to benzyne [Eq. (4)]. The method is more widely applicable to the preparation of reduced indoxazenes, which will be dealt with later (Section II, D).



B. PHYSICAL PROPERTIES

Indoxazene and its methyl derivatives are colorless liquids which can be distilled *in vacuo*. Other indoxazenes, unsubstituted with chromophoric groupings, are for the most part colorless crystalline solids. About 300 indoxazenes, reported in the literature up to the middle of 1965, are listed at the end of the chapter (Tables I–XI).

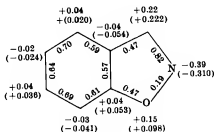


FIG. 1. π -Electron densities and mobile bond orders for indoxazene.⁶⁰ Density values in parentheses are taken from Berthier and Del Re.⁶¹

Spectrochemical data (optical refraction and dispersion) were quoted in support of the structure of indoxazene.^{34, 37, 56, 57} The subject has been well reviewed by Speroni.⁵⁸

⁵⁵ F. Minisci and A. Quilico, *Chim. Ind. (Milan)* **46**, 428 (1964); *Chem. Abstr.* **60**, 15852 (1964).

⁵⁶ K. von Auwers, *Ber. Deut. Chem. Ges.* **57**, 461 (1924).

⁵⁷ P. Grammaticakis, *Bull. Soc. Chim. France* [5] **8**, 101 (1941).

⁵⁸ G. Speroni, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 17, pp. 213–222. Wiley (Interscience), New York, 1962.

The dipole moment is 3.03 D (in benzene)⁵⁹ which agrees fairly well with calculated values (3.1,⁶⁰ 3.53 D⁶¹).

Recently, π electron densities and mobile bond orders have been calculated for the indoxazene system, both by the simple Hückel method,⁶⁰ and by a modified scheme of Berthier and Del Re.⁶¹ The values are given in the accompanying formula (Fig. 1) for comparison.

C. CHEMICAL PROPERTIES

1. Quaternization

Indoxazenes may be quaternized at the nitrogen atom. Dimethyl^{62, 63} and diethyl⁶⁴ sulfate, and benzyl chloride,⁶⁵ have been used. The salts have been isolated as iodides,⁶³ chlorides,⁶⁴ perchlorates,⁶⁵ trichloromercurates,⁶⁴ and, particularly usefully, tetrachloroferrates.^{62, 64, 65} See also Section IV.

2. Electrophilic Substitution

Electrophilic substitution in the indoxazene nucleus proceeds exclusively in the homocyclic ring, whether or not the 3-position is free.

a. *Nitration.* 3-Phenylindoxazene and fuming nitric acid have usually been found to give dinitro products,^{9, 15, 41, 66} frequently as mixtures which were not separated. The 5- and the 4'-(*para* in the phenyl group) positions have been considered to be the most probable sites of substitution,⁹ but this has yet to be confirmed. A small amount of a mononitro derivative, which was not isolated, was also reported.⁹ In the case of 3-phenyl-7-methoxyindoxazene a mononitro compound was obtained, and ascribed the structure **35**.⁶⁷

Nitration of the parent compound with nitrating mixture affords

⁵⁹ K. A. Jensen and F. Friediger, *Kgl. Danske Videnskab. Selskab, Mat.-Fys. Medd.* **20**, No. 20, 1 (1943); *Chem. Zentr.* **I**, 416 (1944).

⁶⁰ G. Del Re, *Tetrahedron* **10**, 81 (1960).

⁶¹ G. Berthier and G. Del Re, *J. Chem. Soc.* p. 3109 (1965).

⁶² A. H. Blatt and N. Gross, *J. Am. Chem. Soc.* **77**, 5424 (1955).

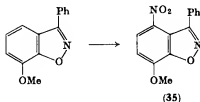
⁶³ S. S. Berg and E. W. Parnell, *J. Chem. Soc.* p. 5275 (1961).

⁶⁴ E. P. Kohler and W. F. Bruce, *J. Am. Chem. Soc.* **53**, 644 (1931).

⁶⁵ J. F. King and T. Durst, *Can. J. Chem.* **40**, 882 (1962).

⁶⁶ Farbwerke, vorm. Meister, Lucius & Brüning, Hoechst, German Patent 65,826 (1892).

⁶⁷ W. Borsche and P. Hahn-Weinheimer, *Ann. Chem.* **570**, 155 (1950).



the 5-nitro derivative,³⁴ but 3-methylindoxazene gave two mononitro compounds, formulated, with reservations, as the 5- and the 7-substituted derivatives.³⁴ In similar compounds with a free 5-position this has generally been taken to be the site of attack,^{13, 34, 39, 68} but nitration at the 7-^{13, 34} and the 6-³⁸ positions has also been claimed. In most cases the structures of the reaction products have not been confirmed in an unequivocal fashion.

b. *Bromination.* The bromination (Br_2/AcOH) of various indoxazenes provides products which likewise have been described as 5-substituted derivatives,^{9, 68} although in one case 4-substitution was reported.⁶⁷ 3-Phenylindoxazene exposed to bromine in a desiccator gave merely a perbromide, which reformed the starting material with water.⁶⁹

c. *Sulfonation.* 3-Phenylindoxazene gave no reaction on warming with concentrated sulfuric acid, but with 40% oleum a disulfonic acid of undetermined structure was formed.⁶⁹

d. *Acylation.* The action of acyl halides on indoxazenes usually results in a ready ring opening (Section II, C, 3, c). In some cases, however, acyl derivatives have been obtained—usually in small yield—and to these 4-substituted structures were attributed.⁶⁷ 7-Methoxy-3-phenylindoxazene is the only compound of this series reported to be smoothly acylated under Friedel-Crafts conditions.⁶⁷

3. Ring Fission

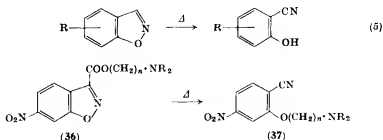
a. *Thermal.* Indoxazenes unsubstituted in the 3-position rearrange very readily to the corresponding salicylonitriles; typically, this occurs soon after melting [Eq. (5)].⁷⁰ Compounds of type **36** form *o*-cyanophenyl ethers (**37**) by decarboxylation and migration of the

⁶⁸ W. Ried and H. Gutjahr, *Chem. Ber.* **86**, 1096 (1953).

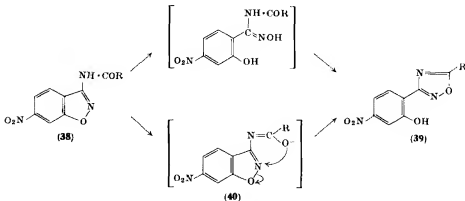
⁶⁹ P. Cohn, *Monatsh. Chem.* **15**, 645 (1894).

⁷⁰ H. Lindemann and H. Cissé, *Ann. Chem.* **469**, 44 (1929).

alkyl group, on prolonged heating in dry toluene.^{71, 72} In the presence of moisture dark-colored products, formulated as ionic compounds, were also obtained.⁷²



b. *With Bases.* The isomerization to salicylonitriles goes particularly easily in the presence of bases. Besides the 3-unsubstituted compounds,^{39, 52} 3-acetamido compounds (38) are also particularly unstable towards alkali. They form the oxadiazoles (39), by a second ring closure,⁷⁰ or a concerted mechanism (40). Substituents in the



benzene ring affect the behavior of indoxazenes towards alkali to only a small extent.⁴⁶

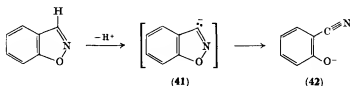
3-Alkyl and 3-aryl compounds are quite stable towards alkali, as are 3-amino derivatives^{46, 70} and derivatives of the 3-carboxylic acid

⁷¹ R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.* **74**, 2226 (1952).

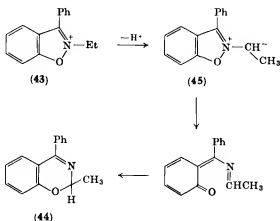
⁷² R. O. Clinton and S. C. Laskowski (Sterling Drug Inc.), U.S. Patent 2,626,261; *Chem. Abstr.* **48**, 733 (1954).

such as the hydrazide and azide.⁷⁰ In contrast, the carboxylic acid itself is decomposed, decarboxylation probably preceding ring opening.^{46,70} The esters are hydrolyzed and then break down analogously.^{27, 29, 46, 68, 73}

The 3-unsubstituted indoxazenes are so unstable towards alkali that it is not possible to prepare them by basic cyclization of oximes.⁷ The same applies to attempted preparations of the 3-carboxylic acid by this route.^{20, 21} The ring opening with alkali probably goes through the carbanion (41), which then undergoes ring opening to form the phenoxy anion (42).⁶⁰



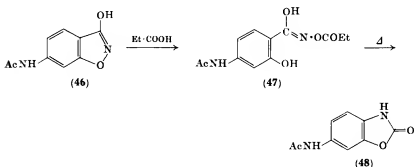
Quaternary salts (43) form benz-1,3-oxazines (44).^{64, 65} The reaction has been formulated as proceeding through ylids (45) and ring-opened products.⁶⁵ See also Section IV.



c. *With Proton and Lewis Acids.* 3-Carboxy-, 3-alkoxycarbonyl-, and 3-carboxamidindoxazenes are broken down to the corresponding

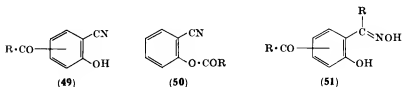
⁷³ J. F. McGhie, C. Morton, B. L. Reynolds, and J. W. Spence, *J. Soc. Chem. Ind. (London)* **68**, 328 (1949); *Chem. Abstr.* **44**, 3466 (1950).

salicylic acids by mineral acids (usually sulfuric).^{27, 30, 46, 74, 75} 3-Hydroxy derivatives are very unstable towards acids; e.g., **46** ring-opens with propionic acid to give an acylated hydroxamic acid (**47**), which on heating undergoes a Beckmann rearrangement and recyclization to the benzoxazolinone (**48**).⁴⁶



Indoxazene itself isomerizes to salicylonitrile in the presence of hydrochloric acid and aluminum chloride.⁶⁷

Acyl halides with 3-unsubstituted indoxazenes give acylsalicylonitriles. The acyl group may be exclusively or chiefly in the ring (**49**) or on the oxygen atom (**50**). 3-Alkyl derivatives, on the other hand, form ring-acylated ketoximes (**51**), besides acylated indoxazenes.⁶⁷



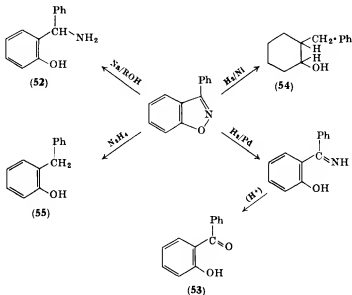
d. *By Reduction* (Scheme 1). Sodium and alcohol reduce 3-phenylindoxazene to *o*-hydroxybenzhydramine (**52**).^{9, 69} Under other conditions (HI/P, 160°) reduction may proceed only as far as the ketimine, which is hydrolyzed to the ketone (**53**),⁷⁶ and the same pathway may be followed catalytically (H₂/Pd/BaSO₄); reduction in dry ether gives the ketimine, but the ketone is obtained in acetic acid.³⁸ With more

⁷⁴ K. G. Rosdahl and E. Degerholm (Aktiebolaget Ferrosan), Swedish Patent 123,563; *Chem. Abstr.* **43**, 6236 (1949).

⁷⁵ Aktieselskabet Ferrosan, British Patent 636,331; *Chem. Abstr.* **44**, 7880 (1950).

⁷⁶ P. Cohn, *Monatsh. Chem.* **17**, 102 (1896).

forcing conditions (H_2 /Raney Ni) the ketone oxygen atom is lost and the phenolic ring reduced, giving the secondary alcohol (54).⁴¹ Hydrazine hydrate at 200° gives *o*-hydroxydiphenylmethane (55), amongst other products.⁹



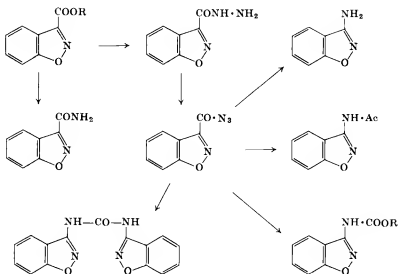
SCHEME 1

4. Reactions of the Substituents

a. *Carboxy Groups.* Many derivatives of indoxazene-3-carboxylic acid have been described. The esters may be saponified in acidic or alkaline media,^{46, 70} or converted into other esters.^{46, 71, 77} With alcoholic ammonia they provide the corresponding amides,^{27, 78} and with hydrazine the hydrazides.^{46, 63, 70} These last give acetyl derivatives.⁷⁰ Their conversion into the corresponding azides^{46, 63, 70} is very important, for from these the amines,^{40, 63, 78} acylamines,^{40, 46, 70} ureas,^{46, 70} and urethanes^{46, 63} are obtained (Scheme 2). We have already noted the easy decarboxylation and ring opening of the carboxylic acids.⁷⁰

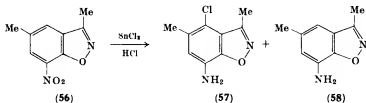
⁷⁷ R. O. Clinton and S. C. Laskowski (Sterling Drug, Inc.), U.S. Patent 2,626,260; *Chem. Abstr.* **48**, 732 (1954).

⁷⁸ H. Lindemann, *Helv. Chim. Acta* **11**, 1027 (1928).



SCHEME 2

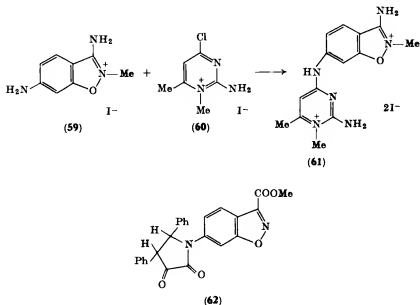
b. *Nitro Groups*. Nitro groups in the 5-^{34, 39} 6-,^{46, 68} and 7-⁴⁰ positions have been reduced to amino groups without opening of the isoxazole ring. Stannous chloride and hydrochloric acid^{34, 39, 40, 46} or Adams catalyst⁶³ have been used. Reduction of **56** with stannous chloride and hydrochloric acid provided a chlorine-containing product (**57**), in addition to the expected amino compound (**58**) (the positions of the substituent groups are not known for certain in these compounds).^{39, 40}



c. *Amino Groups*. Amino groups in the benzene ring of indoxazenes behave as normal aromatic amines, and can be diazotized.^{34, 39, 46, 66-68} The diazonium salts are sometimes fairly stable and isolable.^{39, 46} They couple with naphthols and tertiary aromatic amines,^{34, 39, 66, 68} and on heating form the hydroxy compounds.^{39, 40} For this last

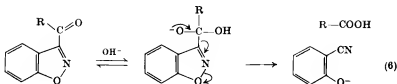
reaction, boiling in water gives a somewhat slow conversion; heating to 150° in sulfuric acid is more efficient. Chloro compounds are obtained by Sandmeyer reactions in the usual way.⁴⁶

Many mono- and bis-acylamino derivatives have been described, for example acetyl,^{34, 40, 46, 68} benzoyl,⁶⁸ and sulfonyl⁶⁸ derivatives. Compounds **59** and **60** give the bismethiodide (**61**).⁶³ Benzaldehyde, phenylpyruvic acid, and 6-amino-3-methoxycarbonylindoxazene give **62**.⁶⁸



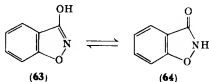
3-Aminoindoxazenes, which are stable towards acids and bases, can be diazotized in acetic acid; Lindemann and Cissée^{46, 70} reported the conversion of 3-amino-5-nitro- and 3-amino-5-acetamido-indoxazenes into the corresponding 3-hydroxy compounds (indoxazenones), via the diazonium salts. Attempts to prepare 3-hydroxyindoxazene and its 6-chloro derivative by the same route were unsuccessful.⁴⁶ The structures of these 3-hydroxy compounds would seem doubtful since Böshagen reports a much higher melting point for 3-hydroxy-5-nitro-indoxazene (223.5,⁴⁶ 85–88°,⁷⁰).

d. *Carbonyl Compounds*. 3-Acylindoxazenes, which give phenylhydrazones in the normal way, are cleaved by alkali to salicylonitrile [Eq. (6)].²⁷



e. *Hydroxy Groups.* 3-Hydroxyindoxazenes have been found to be very easily ring-opened to hydroxamic acid derivatives.^{46, 70}

The tautomeric equilibrium 3-hydroxyindoxazene \rightleftharpoons 2*H*-indoxazen-3-one (**63** \rightleftharpoons **64**) existing in this series has not been studied to date, probably because of the reported instability of the compounds involved. Furthermore, no derivatives of the "fixed forms," e.g., 3-methoxyindoxazene and 2-methylindoxazen-3-one, have yet been prepared. Since 3-hydroxyisoxazoles are known to exist as such,^{79, 80} it seems reasonable to speculate that the same situation might obtain here. In one case (**34**) a positive enol test (FeCl_3) has been reported,⁵⁴ but such evidence is unreliable.



Physiologically active phosphates and thionophosphates have been obtained from 3-hydroxy-⁸¹ and 5-hydroxy-⁸² indoxazenes. 6-Hydroxy compounds are known; they can be acetylated and methylated in the usual ways.³⁹

f. *Sulfonyl Groups.* A disulfonic acid of 3-phenylindoxazene has been converted into the corresponding bis-sulfonyl chloride and amide. A series of salts of the acid were also described.⁶⁹

g. *Cyanines.* Starting from suitable quaternary indoxazenium salts,

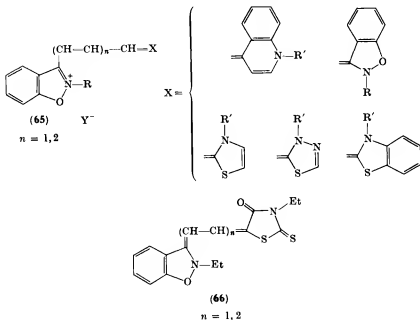
⁷⁹ P. Bravo, G. Gaudiano, A. Quilico, and A. Ricca, *Gazz. Chim. Ital.* **91**, 47 (1961); S. Cabbidu, G. Gaudiano, and A. Quilico, *ibid.* **92**, 501 (1962).

⁸⁰ A. J. Boulton, A. R. Katritzky, A. Majid Hamid, and S. Øksne, *Tetrahedron* **20**, 2835 (1964).

⁸¹ W. Lorenz (Farbenfabriken Bayer A.G.), Belgian Patent 628,347; *Chem. Abstr.* **60**, 12018 (1964).

⁸² T. Harukawa and T. Ishikawa (Takeda Pharmaceutical Industries, Ltd.), Japanese Patent 10,508 (1960); *Chem. Abstr.* **55**, 9441 (1961).

a number of cyanine and merocyanine dyes have been prepared,⁸³ represented by the following general formulas (65, 66):



D. REDUCED DERIVATIVES

1. 4,5,6,7-Tetrahydroindoxazenes

Compounds of this type are regarded as 4,5-disubstituted isoxazoles, and as such they react. Their formation from 2-acylcyclohexanones and hydroxylamine is a special case of the general method of isoxazole formation from β -diketones. 2-Formyl (hydroxymethylene) cyclohexanones, obtained from the respective cyclohexanones and ethyl formate, give 3-unsubstituted derivatives [Eq. (7)].⁸⁴⁻⁹¹ This reaction has been applied to a stereospecific synthesis of estrone.^{87, 89}

⁸³ E. B. Rauch (General Aniline & Film Corp.), Belgian Patent 615,195; *Chem. Abstr.* **57**, 16046 (1962).

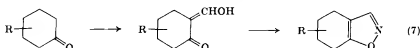
⁸⁴ W. S. Johnson and W. E. Shelberg, *J. Am. Chem. Soc.* **67**, 1745 (1945).

⁸⁵ M. E. Kuehne, *J. Am. Chem. Soc.* **81**, 5400 (1959).

⁸⁶ G. V. Kondrat'eva, L. F. Kudryavtseva, and S. I. Sav'ylov, *Zh. Obshch. Khim.* **31**, 3621 (1961); *Chem. Abstr.* **57**, 8483 (1962).

⁸⁷ D. K. Banerjee and K. M. Sivanandaiah, *Tetrahedron Letters* No. 5, 20 (1960); *J. Indian Chem. Soc.* **38**, 652 (1961); *Chem. Abstr.* **56**, 5867 (1962).

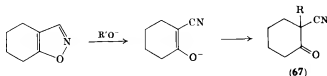
Besides formyl compounds, 2-acetyl,⁹² 2-benzoyl,⁹³ and 2-ethox-
 allyl⁹⁴⁻⁹⁶ cyclohexanones have been cyclized with hydroxylamine, to
 give 3-methyl-, 3-phenyl-, and 3-ethoxycarbonyl-4,5,6,7-tetrahydro-
 indoxazenes, respectively. In some cases the simultaneous formation



of the isomeric 4,5,6,7-tetrahydroanthranils has been observed,^{84,91}
 and it is very likely that in other instances both isomers have been
 formed, but only one reported. If the oxime is prepared and isolated,
 and then cyclized, by-product formation is avoided.⁹¹

A second method of preparation of these compounds is by the 1,3-
 dipolar addition of nitrile oxides to cyclohexanone enamines, followed
 by elimination of the amine (Section II, D, 2, c).

The ready ring fission which is characteristic of 3-unsubstituted
 derivatives of the fully unsaturated compounds is also found here.
 Strong bases (alkali alkoxides) convert them into cyclic β -ketonitriles
 (67, R = H);^{84,85,88,90,91} if methyl iodide is present, a methyl group
 is introduced into the molecule (67, R = CH₃).^{87,89}



⁸⁸ S. Takagi, H. Yasuda, and A. Yokoyama, *Yakugaku Zasshi* **81**, 1639 (1961);
Chem. Abstr. **56**, 8584 (1962).

⁸⁹ D. K. Banerjee and K. M. Sivanandaiah (Indian Institute of Science),
 German Patent 1,134,985; *Chem. Abstr.* **58**, 4473 (1963); Indian Patent
 71,724; *Chem. Abstr.* **58**, 8980 (1963).

⁹⁰ J. DeGraw, L. Goodman, B. Weinstein, and B. R. Baker, *J. Org. Chem.* **27**,
 576 (1962).

⁹¹ K. von Auwers, T. Bahr, and E. Frese, *Ann. Chem.* **441**, 54 (1925).

⁹² H. Smith, *J. Chem. Soc.* p. 803 (1953).

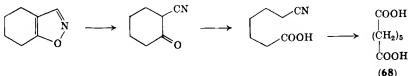
⁹³ L. I. Smith and R. M. Scribner, *J. Am. Chem. Soc.* **78**, 3412 (1956).

⁹⁴ U. P. Basu and S. P. Dhar, *J. Indian Chem. Soc.* **23**, 189 (1946); *Chem. Abstr.*
41, 2416 (1947).

⁹⁵ H. Kano and K. Ogata (Shionogi & Co., Ltd.), Japanese Patent 18,383
 (1963); *Chem. Abstr.* **60**, 2936 (1964).

⁹⁶ H. Kano, M. Ogata, R. Kido, and K. Yamamoto (Shionogi & Co., Ltd.),
 French Patent M 1621; *Chem. Abstr.* **58**, 12568 (1963).

The parent compound also undergoes a further ring fission with sodium ethoxide, finally yielding pimelic acid (**68**).⁹¹ Adipic acid is obtained using alkaline hydrogen peroxide.⁸⁸



Derivatives of the 3-carboxylic acid are noteworthy. Esters,⁹⁴⁻⁹⁶ the acid chloride,⁹⁴ amide,⁹⁴ and the hydrazide and several of its derivatives⁹⁶⁻⁹⁸ have been prepared, and the amide has been converted into the 3-amino compound,⁹⁹ sulfonamides of which have been described.¹⁰⁰

2. Other Reduced Derivatives

a. *4,5-Dihydroindoxazenes*. The preparation and properties of these compounds parallel those of the tetrahydro derivatives, being formed with compounds of types **69**¹⁰¹ and **70**^{84, 88, 102} as starting materials. They form unsaturated cyclic β -ketonitriles (**71**, R = H) with alkoxides,^{84, 88, 101, 102} which again may be methylated with methyl iodide (giving **71**, R = CH₃),^{87, 89} or the second ring opened with alkaline peroxide (giving **72**).⁸⁸

⁹⁷ H. Kano, M. Ogata, R. Kido, and K. Yamamoto (Shionogi & Co., Ltd.), U.S. Patent 3,073,840; *Chem. Abstr.* **59**, 633 (1963); Japanese Patent 12,932 (1963) *Chem. Abstr.* **60**, 2935 (1964).

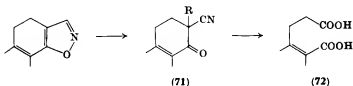
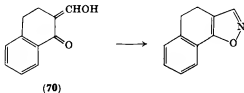
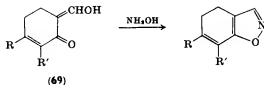
⁹⁸ H. Kano, M. Ogata, R. Kido, and K. Yamamoto (Shionogi & Co. Ltd.), Japanese Patents 629 and 630 (1964); *Chem. Abstr.* **60**, 10687 (1964). H. Kano, M. Ogata, and I. Adachi, *Shionogi Kenkyusho Nempo* **14**, 44 (1964); *Chem. Abstr.* **62**, 7743 (1965).

⁹⁹ Shionogi & Co., Ltd., British Patent 875,458; *Chem. Abstr.* **56**, 8720 (1962); H. Kano, I. Kikkawa, Y. Makisumi, S. Takahashi, and H. Ogata (Shionogi & Co., Ltd.), Japanese Patent 4887 (1962); *Chem. Abstr.* **59**, 1644 (1963).

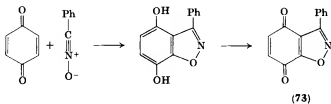
¹⁰⁰ I. Satoda, T. Fukui, and K. Mori (Nippon Shinyaku Co.), Japanese Patent 2679 (1961); *Chem. Abstr.* **55**, 27377 (1961). In the Abstract there is a discrepancy between the title and the structural formula given. The compounds may in fact be 3-sulfonamido-4,5,6,7-tetrahydroanthranils.

¹⁰¹ W. M. Johnson and R. E. Ireland (Wisconsin Alumni Research Foundation), U.S. Patent 2,842,559; *Chem. Abstr.* **53**, 3156 (1959).

¹⁰² K. von Auwers and A. E. Nold, *J. Prakt. Chem.* [2] **150**, 57 (1937).



b. *4,7-Dihydroindoxazenes*. The addition of benzonitrile oxide to *p*-quinones leads to 4,7-dihydroxyindoxazenes, which are readily oxidized by atmospheric oxygen or excess of quinone to indoxazene-4,7-quinones (73) (systematically regarded as derivatives of the 4,7-dihydro compound).¹⁰³ These compounds are stable towards acids, including oxidizing acids, but are decomposed by permanganate and by hot alkalis.¹⁰³

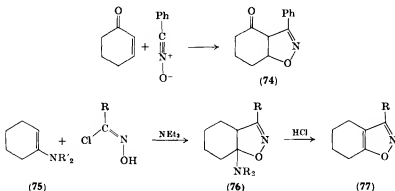


c. *3a,4,5,6,7,7a-Hexahydroindoxazenes*. An example (74) of this series was obtained by Quilico¹⁰⁴ by addition of benzonitrile oxide to cyclohex-2-en-1-one. Cyclohexene and its 1-methyl and 1-phenyl

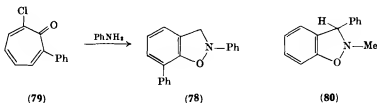
¹⁰³ A. Quilico and G. S. D'Alcontres, *Gazz. Chim. Ital.* **80**, 140 (1950).

¹⁰⁴ N. Barbulescu, P. Grünanger, M. R. Langella, and A. Quilico, *Tetrahedron Letters* p. 89 (1961).

derivatives do not react with nitrile oxides, but cyclohexanone enamines (75) give addition products (76) which may be converted into 4,5,6,7-tetrahydroindoxazenes (77) by acids.¹⁰⁵ (See also Section IV.)



d. *2,3-Dihydroindoxazenes*. A benzisoxazoline (78) was reported as being formed by the action of aniline on an α -chlorotropone (79).¹⁰⁶ Huisgen and Knorr¹⁰⁷ obtained a further example (80) by generation of benzyne in the presence of a nitron.



E. APPLICATIONS

A number of indoxazenes show physiological activity and have been tested for pharmacological use. Some 4,5,6,7-tetrahydro derivatives, for instance, were tried as analeptics.⁹⁴ Compounds such as 61 show trypanocidal activity,⁶³ while derivatives of 6-acetamidindoxazene-

¹⁰⁵ G. Bianchetti, D. Pocar, and P. Dalla Croce, *Gazz. Chim. Ital.* **93**, 1726 (1963); M. E. Kuehne, S. J. Weaver, and P. Franz, *J. Org. Chem.* **29**, 1582 (1964).

¹⁰⁶ T. Mukai, *Bull. Chem. Soc. Japan* **32**, 272 (1959); *Chem. Abstr.* **54**, 3349 (1960).

¹⁰⁷ R. Huisgen and R. Knorr, *Naturwissenschaften* **48**, 716 (1962).

3-carboxylic acid are tuberculostatic,¹⁰⁸ and a series of 3-amino-indoxazenes have been found to show sedative and analgesic properties.⁴⁴ Some indoxazene thionophosphates seem promising as insecticides.⁸¹

Reference has already been made (Section II, A, 1, *b*) to the use of 6-nitroindoxazene-3-carboxylate ester as an intermediate in the preparation of substituted salicylic acids.

Cyanine dyes in this series have been described as photographic sensitizers, and are strongly adsorbed on the silver bromide crystals. The sensitization maximum is at about 500–650 m μ .⁸³

III. 2,1-Benzisoxazoles (Anthranils)

A. FORMATION

Two basic routes are available for the synthesis of the anthranil ring system:

- (1) cyclizations of types **81** and **82**, in which the 1—2 or 2—3 bond is formed, and
- (2) introduction of C-3, forming bonds 2—3 and 3—3a (**83**).



Besides these two main types, there are a number of other less general synthetic methods.

1. Closure of Bonds 1—2 or 2—3

a. *By Reduction of o-Nitrobenzoyl Compounds.* On reduction, *o*-nitrobenzaldehyde^{109–112} and its substituted derivatives^{113–118}

¹⁰⁸ C. van der Stelt, A. J. Zwart Voorspuij, and W. T. Nauta, *Arzneimittelforsch.* **4**, 544 (1954); *Chem. Abstr.* **49**, 10887 (1955).

¹⁰⁹ P. Friedländer and R. Henriques, *Ber. Deut. Chem. Ges.* **15**, 2105 (1882).

¹¹⁰ P. Friedländer, *Ber. Deut. Chem. Ges.* **15**, 2572 (1882).

¹¹¹ P. Carré, *Ann. Chim. (Paris)* [8] **6**, 408 (1905).

¹¹² H. Goldschmidt and E. Sunde, *Z. Physik. Chem.* **56**, 1 (1906).

¹¹³ O. Prinz, *J. Prakt. Chem.* [2] **24**, 353 (1881).

¹¹⁴ C. Liebermann, *Ber. Deut. Chem. Ges.* **19**, 351 (1886).

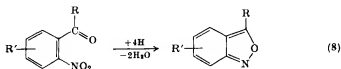
¹¹⁵ H. Grüne, *Ber. Deut. Chem. Ges.* **19**, 2299 (1886).

¹¹⁶ K. Elber, *Ber. Deut. Chem. Ges.* **19**, 2306 (1886).

¹¹⁷ P. Friedländer and W. Schreiber, *Ber. Deut. Chem. Ges.* **28**, 1382 (1895).

¹¹⁸ F. Faltis and F. Kloiber, *Monatsh. Chem.* **53/54**, 620 (1929).

o-nitroacetophenones,¹¹⁹⁻¹²⁵ *o*-nitrobenzophenones,^{122,126-128} and heterocyclic *o*-nitrobenzoyl compounds¹²⁹⁻¹³¹ give the corresponding anthranils, mostly in good yields [Eq. (8)]. The following reducing agents have been used: stannous chloride or tin and hydrochloric acid,^{112-116, 118, 120, 123, 125, 127, 131, 132} tin and acetic acid,^{109,126} zinc and acetic^{117, 122, 133} or hydrochloric^{119, 129} acid, ammonia,¹⁰⁹ ammonium chloride^{120, 122} or soda lime,¹²⁰ ammonium sulfide,¹¹³ sodium sulfide,¹²⁸ ferrous sulfate and ammonia,¹¹⁰ sodium amalgam,¹²⁰ sodium alkoxides,¹¹¹ sodium dithionite,¹³⁴ trialkyl phosphites,¹³⁵ and hydrogen with platinum^{125, 136} or palladium¹³⁶ catalysts. Since further reduction leads to *o*-aminobenzoyl compounds^{110, 123, 131} (Section III, C, 4, c), choice of reducing agent is often critical.



o-Nitrobenzaldehyde acetals may also be used, with aluminum amalgam¹³⁷ or zinc and acetic acid¹³⁸ as reducing agents. A 7,7'-

¹¹⁹ R. Camps, *Ber. Deut. Chem. Ges.* **32**, 29 (1899).

¹²⁰ R. Camps, *Arch. Pharm.* **240**, 423 (1902).

¹²¹ E. Bamberger, *Ber. Deut. Chem. Ges.* **36**, 819 (1903).

¹²² E. Bamberger and F. Elger, *Ber. Deut. Chem. Ges.* **36**, 1611 (1903).

¹²³ B. E. Christensen, B. Graham, and A. M. Griffith, *J. Am. Chem. Soc.* **67**, 2001 (1945).

¹²⁴ J. C. E. Simpson, *J. Chem. Soc.* p. 94 (1946).

¹²⁵ C. H. Wang, R. Isensee, A. M. Griffith, and B. E. Christensen, *J. Am. Chem. Soc.* **69**, 1909 (1947).

¹²⁶ E. Bamberger and S. Lindberg, *Ber. Deut. Chem. Ges.* **42**, 1723 (1909).

¹²⁷ J. Tirouflet, *Bull. Soc. Sci. Bretagne, Spec. No.* **26**, 7 (1951); *Chem. Abstr.* **47**, 8694 (1953).

¹²⁸ F. Korte and O. Behner, *Ann. Chem.* **621**, 51 (1959).

¹²⁹ W. Steinkopf and E. Günther, *Ann. Chem.* **522**, 28 (1936).

¹³⁰ A. A. Morton and D. Bannerman, *J. Am. Chem. Soc.* **67**, 1503 (1945).

¹³¹ A. J. Nunn and K. Schofield, *J. Chem. Soc.* p. 583 (1952).

¹³² C. Mannich and G. Berger, *Arch. Pharm.* **277**, 117 (1939).

¹³³ G. Heller, *J. Prakt. Chem.* [2] **77**, 145 (1908).

¹³⁴ H. H. Hodgson and H. G. Beard, *J. Soc. Chem. Ind. (London)* **45**, 93 T (1926).

¹³⁵ Altaf-ur-Rahman and A. J. Boulton, *Tetrahedron, Suppl.* **7**, 49 (1966).

¹³⁶ K. W. Merz and J. Hotzel, *Arch. Pharm.* **274**, 292 (1936).

¹³⁷ E. Bamberger and F. Elger, *Ber. Deut. Chem. Ges.* **36**, 3645 (1903).

¹³⁸ G. Heller, *Ber. Deut. Chem. Ges.* **43**, 1907 (1910).

dianthranilyl has also been prepared.¹³⁹ Wolff-Kishner reduction of *o*-nitrobenzaldehyde gives a little anthranil as a by-product.¹⁴⁰

The first anthranil ("azo-opianic acid") was made by this method in 1881,¹¹³ but was not recognized as such. In 1882 Friedländer and Henriques¹⁰⁹ prepared the parent compound, by reduction of *o*-nitrobenzaldehyde with tin and acetic acid. They thought it to be the anhydride of anthranilic acid, and hence arose the name "anthranil."

It has been shown, using O¹⁸, that the carbonyl oxygen is lost, and the cyclic oxygen atom is derived from the nitro group, in the reductive cyclization.¹⁴¹

Reduction of *o*-nitrophenylglyoxylic acid with zinc and acetic acid¹⁴² or ammonia,¹⁴³ or with stannous chloride and hydrochloric acid,¹⁴² gives anthranil-3-carboxylic acid (84), which is also known as anthroxanic acid.

2,1-Benzisoxazolin-3-ones (85, R = H) have been obtained by reduction of *o*-nitrobenzoic acids or their derivatives, using tin,^{143,144} zinc,¹⁴⁵ or stannous chloride,¹⁴⁵ and hydrochloric acid, or zinc with acetic acid¹³⁸ or baryta,¹⁴⁶ or electrolytic methods.^{147,148} Ciamician and Silber¹⁴⁹ found that irradiation of *o*-nitrobenzaldehyde in paraldehyde gave 85 (R = Ac), among other products. Recently, Musso and Schröder¹⁵⁰ isolated 3-aminoanthranil as an intermediate in the catalytic reduction of *o*-nitrobenzonitrile to *o*-aminobenzamide [Eq. (9)].

Reduction of *o*-nitrobenzophenone with aluminum amalgam or electrolytically gives 3-phenyl-1,3-dihydroanthranil (86).¹⁵¹ A claim

¹³⁹ K. Elbs and H. Lerch, *J. Prakt. Chem.* [2] **93**, 1 (1916).

¹⁴⁰ W. Seibert, *Chem. Ber.* **81**, 266 (1948).

¹⁴¹ I. I. Kukhtenko, *Dokl. Akad. Nauk SSSR* **132**, 609 (1960); *Chem. Abstr.* **54**, 24619 (1960).

¹⁴² E. Bamberger and S. Lindberg, *Ber. Deut. Chem. Ges.* **43**, 122 (1910).

¹⁴³ G. Heller, *Ber. Deut. Chem. Ges.* **44**, 2418 (1911).

¹⁴⁴ S. Gabriel and A. Thieme, *Ber. Deut. Chem. Ges.* **52**, 1079 (1919).

¹⁴⁵ J. M. Woolley (Imperial Chemical Industries Ltd.), U.S. Patent 2,846,307; *Chem. Abstr.* **53**, 5933 (1959).

¹⁴⁶ E. Bamberger and F. L. Pyman, *Ber. Deut. Chem. Ges.* **42**, 2297 (1909).

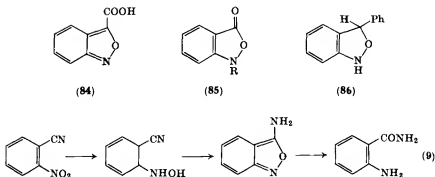
¹⁴⁷ K. Gleu and K. Pfannstiel, *J. Prakt. Chem.* [2] **146**, 129 (1936).

¹⁴⁸ M. Le Guyader and D. Peltier, *Compt. Rend.* **253**, 2544 (1961); M. Le Guyader, A. Tallec, and R. Legoff, *Compt. Rend.* **258**, 6175 (1964).

¹⁴⁹ G. Ciamician and P. Silber, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis. Mat. Nat.* [5] **10**, I, 232 (1901); [5] **11**, II, 150 (1902); *Ber. Deut. Chem. Ges.* **34**, 2045 (1901); *Gazz. Chim. Ital.* **33**, I, 354 (1903).

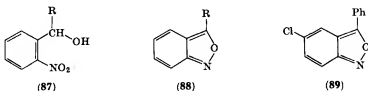
¹⁵⁰ H. Musso and H. Schröder, *Chem. Ber.* **98**, 1562 (1965).

¹⁵¹ C. Baezner and A. Gardiol, *Ber. Deut. Chem. Ges.* **39**, 2513 (1906).



to have prepared an analogous methyl derivative¹⁵² was later refuted.¹³⁷

b. *By Reduction of o-Nitrobenzyl Alcohols.* Anthranil is formed, amongst other products, on reduction of *o*-nitrobenzyl alcohol (87, R=H) with zinc and alkali^{153, 154} or with sodium alkoxide.¹⁵⁵ *o*-Nitromandelic acid (87, R=COOH) and its nitrile (87, R=CN) give anthroxanic acid (88, R=COOH) with a variety of reducing agents;¹⁵⁶⁻¹⁵⁹ the nitrile forms anthroxanamide (88, R=CONH₂) with zinc and hydrochloric acid.¹⁶⁰



o-Nitrobenzhydrol (87, R=Ph) cyclizes with introduction of a chlorine atom on heating with thionyl chloride in chloroform, forming 5-chloro-3-phenylanthranil (89).¹⁶¹

¹⁵² H. Wislicenus, *J. Prakt. Chem.* [2] **54**, 18 (1896).

¹⁵³ P. Freundler, *Bull. Soc. Chim. France* [3] **31**, 878 (1904).

¹⁵⁴ P. Carré, *Compt. Rend.* **140**, 664 (1905).

¹⁵⁵ P. Carré, *Bull. Soc. Chim. France* [3] **33**, 1161 (1905).

¹⁵⁶ G. Heller, *Ber. Deut. Chem. Ges.* **39**, 2339 (1906).

¹⁵⁷ Kalle & Co., A.G., German Patent 191,855; *Chem. Abstr.* **2**, 1636 (1908).

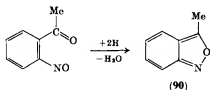
¹⁵⁸ Kalle & Co., A.G., German Patent 195,812; *Chem. Abstr.* **2**, 2304 (1908).

¹⁵⁹ G. Heller, *Ber. Deut. Chem. Ges.* **43**, 2892 (1910).

¹⁶⁰ A. Reissert and K. Hessert, *Ber. Deut. Chem. Ges.* **57**, 964 (1924).

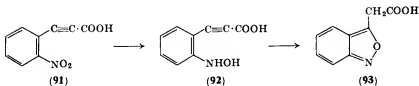
¹⁶¹ W. B. Dickinson, *J. Am. Chem. Soc.* **86**, 3580 (1964).

c. *By Reduction of o-Nitrosobenzoyl Compounds.* *o*-Nitrosoacetophenone may be reduced to 3-methylanthranil (**90**) with zinc and acetic acid.¹³³



d. *Further Reductive Methods.* The so-called agnotobenzaldehyde, an intermediate reduction product of *o*-nitrobenzaldehyde, forms anthranil with aluminum amalgam, or spontaneously on standing, with or without mineral acids, or on steam-distillation.¹⁶²

o-Nitrophenylpropionic acid (**91**), with zinc and ammonia, gives the corresponding hydroxylamino compound (**92**), which isomerizes to anthranil-3-acetic acid (homoanthroxanic acid, **93**).¹⁶³ Later, arguments were raised against structure (**93**),¹⁶⁴ but a recent reinvestigation,¹⁶⁵ using spectroscopic techniques, has vindicated the original formulation.



e. *Oxidative Methods.* These are less widely applicable to the preparation of anthranils, but a few examples are available. *o*-Aminobenzaldehyde,^{120,166} aromatic *o*-aminoketones,^{126,137} and isatic acid¹⁴² may be oxidized to the corresponding anthranil with Caro's acid,^{126,137,142,166} or 30% hydrogen peroxide¹⁶⁷ [Eq. (10)]. More highly condensed systems (**94**, **95**) may be obtained by hypobromite oxidation of 1-amino- and 1,5-diaminoanthraquinone.¹⁶⁸

Certain oximes of *o*-aminoketones with the required stereochemistry

¹⁶² E. Bamberger, *Ber. Deut. Chem. Ges.* **39**, 4252 (1906).

¹⁶³ G. Heller and W. Tischner, *Ber. Deut. Chem. Ges.* **42**, 4555 (1909).

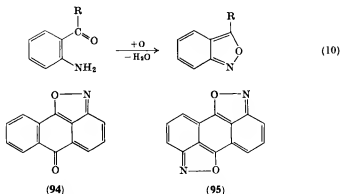
¹⁶⁴ F. Arndt, L. Ergener, and O. Kutlu, *Chem. Ber.* **86**, 957 (1953).

¹⁶⁵ J. L. Pinkus, unpublished work, 1963-4.

¹⁶⁶ E. Bamberger and E. Demuth, *Ber. Deut. Chem. Ges.* **36**, 829 (1903).

¹⁶⁷ E. Bamberger, *Helv. Chim. Acta* **7**, 814 (1924).

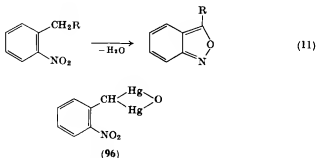
¹⁶⁸ Farbenfabriken, vorm. Bayer & Co., German Patent 335,160; *Chem. Zentr.* **II**, 937 (1921).



may be converted into anthranils by diazotization and heat treatment (17→19, p. 283).³⁶

Other methods, involving neither external oxidation nor reduction, may be classified according to the starting materials employed.

f. *From o-Nitrotoluenes*. Although the formation of anthranil by the action of sodium hydroxide on *o*-nitrotoluene [Eq. (11), R=H] has been described in the Patent literature,¹⁶⁹ later experiments failed to substantiate this finding,¹⁷⁰ and it would seem a somewhat unpromising method in view of the instability of anthranil towards alkali (Section III, C,4, a). However, the conversion can be effected in the presence of mercuric oxide,¹⁷¹ when a mercury-containing intermediate, formulated as 96, is isolated and converted into anthranil with dilute hydrochloric acid.^{172,173}



¹⁶⁹ Kalle & Co., A.G., German Patent 194,811; *Chem. Abstr.* 2, 2304 (1908).

¹⁷⁰ R. Scholl, *Monatsh. Chem.* 34, 1011 (1913).

¹⁷¹ Kalle & Co., A.G., German Patent 194,364; *Chem. Zentr.* I, 1346 (1908).

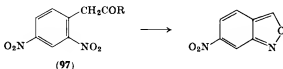
¹⁷² Kalle & Co., A.G., German Patent 199,317; *Chem. Zentr.* II, 210 (1908).

¹⁷³ A. Reissert, *Ber. Deut. Chem. Ges.* 40, 4209 (1907).

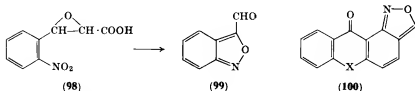
The conversion by alkali of *o*-nitrotoluene into anthranilic acid most probably goes via anthranil as an intermediate.^{170,174} In the acid, one oxygen atom arises from the nitro group, the other from the alkaline medium.^{141,175}

o-Nitrodiarylmethanes form 3-arylanthranils on heating in paraffin oil to 300° [Eq. (11), R = Ar].¹⁷⁶ The yield, however, is poor, because the products isomerize readily to acridones at high temperatures (Section III, C, 5, a).

Substituted *o*-nitrophenylacetic acids have been reported to give anthroxanic acids on heating with aqueous sodium hydroxide¹⁷⁷ or with phosphorus pentachloride in benzene.¹⁷⁸ Amides react similarly.¹⁷⁸ 6-Nitroanthranils are produced by the action of hot concentrated sulfuric acid on 2,4-dinitrophenylacetic acid (**97**, R = OH)¹⁷⁹ and 2,4-dinitrophenylacetones (e.g., **97**, R = CH₃);¹⁸⁰⁻¹⁸² the carbonyl substituent is lost in the reaction.



Steam distillation of the glycidic acid (**98**)^{178,183} proceeds with elimination of water and carbon dioxide to give 3-formylanthranil (anthroxanaldehyde, **99**).¹⁸³



¹⁷⁴ G. Lock, *Ber. Deut. Chem. Ges.* **73B**, 1377 (1940).

¹⁷⁵ A. I. Brodskii, I. P. Gragerow, I. F. Franchuk, L. V. Sulima, I. I. Kukhtenko, V. A. Lunenok, A. S. Fomenko, and M. M. Aleksankin, *Tr. Tashkentsk. Konf. po Mirnomu Ispolz. At. Energii, Akad. Nauk Uz. SSR* **2**, 327 (1960); *Chem. Abstr.* **57**, 9258 (1962).

¹⁷⁶ A. Kliegl, *Ber. Deut. Chem. Ges.* **42**, 591 (1909).

¹⁷⁷ J. M. Gulland, *J. Chem. Soc.* p. 2872 (1931).

¹⁷⁸ D. H. Hey and A. L. Palluel, *J. Chem. Soc.* p. 4123 (1956).

¹⁷⁹ M. C. Garg, *J. Org. Chem.* **27**, 3683 (1962).

¹⁸⁰ S. S. Joshi and I. R. Gambhir, *J. Am. Chem. Soc.* **78**, 2222 (1956).

¹⁸¹ S. S. Joshi and I. R. Gambhir, *J. Org. Chem.* **26**, 3714 (1961).

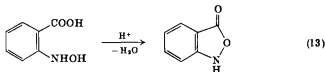
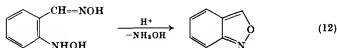
¹⁸² I. R. Gambhir and S. S. Joshi, *J. Indian Chem. Soc.* **41**, 43 (1964).

¹⁸³ A. Schillinger and S. Wleügel, *Ber. Deut. Chem. Ges.* **16**, 2222 (1883).

Finally, a series of *o*-nitroalkylantraquinones¹⁸⁴ and *o*-nitroalkylthiaxanthone-1,1-dioxides¹⁸⁵ have been converted with fuming sulfuric acid into condensed anthranils (e.g., **100**, X = CO, SO₂).

g. *From o-Nitrosobenzyl Alcohols.* Anthranil is formed by loss of water from *o*-nitrosobenzyl alcohol,^{121,186} and *o*-nitrosomandelonitrile with concentrated hydrochloric acid forms anthroxanic acid, hydrolysis occurring under the reaction conditions.¹⁸⁶

h. *From o-Hydroxylaminobenzoyl Compounds.* Acids convert *o*-hydroxylaminobenzaldoxime into anthranil [Eq. (12)],^{121,122} and under similar conditions 2,1-benzisoxazolin-3-one is formed from *o*-hydroxylaminobenzoic acid [Eq. (13)].¹⁴⁶ *o*-Hydroxylaminobenzo-nitrile isomerizes in ethanol into 3-aminoanthranil.¹⁶⁰



o-Aminobenzoic acids cannot be dehydrated directly to anthranils. The formerly so-called "acylanthranils," obtained from acylanthranilic acids, contain a different heterocyclic nucleus (Section III, C, 5, e).

i. *From o-Azidobenzoyl Compounds.* Aromatic *o*-azido aldehydes¹⁸⁷ and ketones^{135,188} may be decomposed by heating in water,¹⁸⁷ or in decalin¹⁸⁸ or acetic acid¹³⁵ solution, or without solvent,¹⁸⁷ giving

¹⁸⁴ K. Wilke, U.S. Patent 1,417,875 (1922); *Chem. Abstr.* **16**, 2696 (1922); Farbwerke, vorm. Meister, Lucius & Brüning, Hoechst, German Patent 360,422 (1922); German Patent 364,181 (1922); *Chem. Zentr.* **II**, 190 (1923); K. Wilke (I.G. Farbenindustrie, A.G.), German Patent 464,863; *Chem. Zentr.* **II**, 1623 (1928).

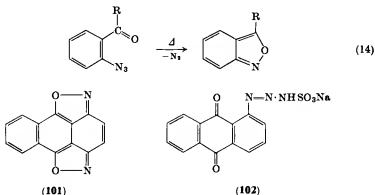
¹⁸⁵ Badische Anilin und Soda-Fabrik A.G., British Patent 790,587; *Chem. Abstr.* **52**, 15593 (1958).

¹⁸⁶ E. Bamberger, *Ber. Deut. Chem. Ges.* **36**, 836 (1903).

¹⁸⁷ E. Bamberger and E. Demuth, *Ber. Deut. Chem. Ges.* **34**, 3874 (1901).

¹⁸⁸ P. A. S. Smith, B. B. Brown, R. K. Putney, and R. F. Reinisch, *J. Am. Chem. Soc.* **75**, 6335 (1953).

anthranils with loss of nitrogen [Eq. (14)]. α -Azidoanthraquinones give condensed anthranils (**94**, **95**, **101**) in an analogous manner;¹⁸⁹⁻¹⁹² here nitrogen evolution sometimes occurs spontaneously. The preparation of the azide used to make **94** may be effected by the action of alkali on **102**.¹⁹³



j. *From o-Nitrobenzaldehydes and Aromatic Compounds.* The reaction between *o*-nitrobenzaldehyde^{194, 195} or 2,4-dinitrobenzaldehyde¹⁹⁵⁻¹⁹⁹ and benzene,^{194, 196, 200, 201} toluene,¹⁹⁸ naphthalene,¹⁹⁵ or fluoro-,¹⁹⁸ chloro-,^{195, 197} bromo-,¹⁹⁵ or iodo-¹⁹⁹ benzene, in the presence of concentrated sulfuric acid, leads to 3-arylanthranils [Eq. (15)], along with various products of the acridine series.

¹⁸⁹ A. Schaarschmidt, A. Constandachi, and M. Thiele, *Ber. Deut. Chem. Ges.* **49**, 1632 (1916).

¹⁹⁰ K. Brass and F. Albrecht, *Ber. Deut. Chem. Ges.* **61B**, 983 (1928).

¹⁹¹ L. Gattermann and R. Ebert, *Ber. Deut. Chem. Ges.* **49**, 2117 (1916).

¹⁹² L. Gattermann and R. Rolfes, *Ann. Chem.* **425**, 135 (1921).

¹⁹³ D. Z. Zawel'skii and L. A. Lishnevskaya, *Zh. Obshch. Khim.* **28**, 745 (1958); *Chem. Abstr.* **52**, 17209 (1958).

¹⁹⁴ A. Kliegl, *Ber. Deut. Chem. Ges.* **41**, 1845 (1908).

¹⁹⁵ I. Tănăsescu and Z. Frenkel, *Bull. Soc. Chim. France* p. 693 (1960); I. Tănăsescu, M. Ionescu, I. Goia, and H. Mantsch, *ibid.* p. 698 (1960).

¹⁹⁶ I. Tănăsescu and E. Ramontianu, *Bull. Soc. Chim. France* [4] **53**, 918 (1933).

¹⁹⁷ F. R. Bradbury and W. H. Linnell, *J. Chem. Soc.* p. 377 (1942).

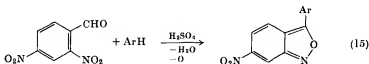
¹⁹⁸ I. Tănăsescu, L. Almási, and A. Hantz, *Acad. Rep. Populare Romine, Filiala Cluj, Studii Cercetari Chim.* **11**, 105 (1960); *Chem. Abstr.* **55**, 11415 (1961).

¹⁹⁹ I. Tănăsescu and Z. Frenkel, *Studia Univ. Babes-Bolyai, Ser. Chim.*, **2**, 145 (1959); *Chem. Abstr.* **55**, 5496 (1961).

²⁰⁰ I. Tănăsescu, *Bull. Soc. Chim. France* [4] **41**, 528 (1927).

²⁰¹ I. Tănăsescu and M. Macarovici, *Bull. Soc. Chim. France* [4] **53**, 372 (1933).

The reaction is certainly a complex one, and involves a reduction stage. Tanasescu's proposed mechanism, via anthranil-*N*-oxides,²⁰²⁻²⁰⁷ has been assailed from many quarters,²⁰⁸⁻²¹³ particularly as regards its postulation of *o*-nitrobenzaldehyde tautomerism, and the question cannot yet be considered as settled.



Anisole and benzonitrile gave no anthranils with dinitrobenzaldehyde in sulfuric acid,¹⁹⁶ but aniline could be condensed with *o*-nitrobenzaldehyde in the presence of zinc chloride;²¹⁴⁻²¹⁶ triaryl methane derivatives are formed as by-products. Phosphorus oxychloride has also served as a condensing agent.²¹⁷ Phenols²¹⁸⁻²²¹ and dimethylaniline²²² react with *o*-nitrobenzaldehydes, in the presence of hydrogen chloride in acetic acid^{218, 219, 222} or ether,²²¹ or of hydrogen bromide,²²¹ giving 3-arylanthranils. Usually a halogen atom is introduced into the

²⁰² I. Tănăsescu, *Bull. Soc. Chim. France* [4] **39**, 1443 (1926).

²⁰³ I. Tănăsescu, *Bull. Soc. Chim. France* [4] **41**, 1468 (1927).

²⁰⁴ I. Tănăsescu, *Bull. Soc. Chim. France* [4] **41**, 1497 (1927).

²⁰⁵ I. Tănăsescu, *Bull. Soc. Chim. France* [4] **43**, 1118 (1928).

²⁰⁶ I. Tănăsescu and M. Macarovici, *Bull. Soc. Chim. France* [4] **49**, 1295 (1931).

²⁰⁷ I. Tănăsescu, *Bull. Soc. Chim. France* [4] **53**, 381 (1933).

²⁰⁸ H. Gilman and R. E. Fothergill, *J. Am. Chem. Soc.* **49**, 2815 (1927).

²⁰⁹ F. Arndt, *Ber. Deut. Chem. Ges.* **61**, 1125 (1928).

²¹⁰ F. Arndt, *Ber. Deut. Chem. Ges.* **62**, 1167 (1929).

²¹¹ H. Gilman and R. E. Fothergill, *Bull. Soc. Chim. France* [4] **45**, 1132 (1929).

²¹² I. Y. Postovskii and B. K. Uparov, *J. Russ. Phys. Chem. Soc.* **61**, 719 (1929); *Chem. Zentr.* **II**, 427 (1931); *Chem. Abstr.* **23**, 4941 (1929).

²¹³ K. Lehmstedt, *Ber. Deut. Chem. Ges.* **67B**, 336 (1934).

²¹⁴ I. Tănăsescu and A. Silberg, *Bull. Soc. Chim. France* [4] **51**, 1357 (1932).

²¹⁵ I. Tănăsescu and M. Suci, *Bull. Soc. Chim. France* [5] **3**, 1753 (1936).

²¹⁶ I. Tănăsescu and M. Suci, *Bull. Soc. Chim. France* [5] **4**, 245 (1937).

²¹⁷ I. Tănăsescu, C. Anghel, and A. Popescu, *Studia Univ. Babes-Bolyai, Ser. Chim.* **9**, 89 (1964); *Chem. Abstr.* **61**, 16004 (1964).

²¹⁸ A. Guyot and A. Haller, *Bull. Soc. Chim. France* [3] **31**, 530 (1904).

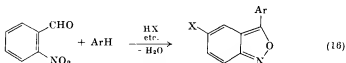
²¹⁹ T. Zincke and K. Siebert, *Ber. Deut. Chem. Ges.* **39**, 1930 (1906).

²²⁰ I. S. Ioffe and B. G. Belen'kii, *Zh. Obshch. Khim.* **23**, 1525 (1953); *Chem. Abstr.* **48**, 1686 (1954).

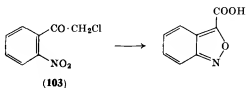
²²¹ J. D. Loudon and G. Tennant, *J. Chem. Soc.* p. 3092 (1962).

²²² T. Zincke and W. Prenntzell, *Ber. Deut. Chem. Ges.* **38**, 4116 (1905).

anthranil nucleus at the same time;²¹⁵⁻²²² in these cases the necessity for a reduction stage in the mechanism does not arise [Eq. (16)].

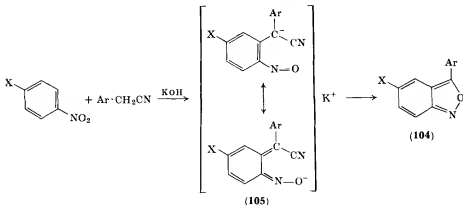


k. *Other Methods.* Formation of anthroxanic acid by the action of base on ω -chloro-*o*-nitroacetophenone (**103**) formally involves an internal oxidation-reduction process.²²³



2. Formation of Bonds 2—3 and 3—3a

p-Halonitrobenzenes react with benzyl cyanides in the presence of a large excess of methanolic potassium hydroxide to give 3-aryl-5-haloanthranils (**104**). The intermediate **105** has been isolated.^{224, 225}



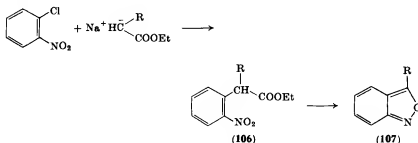
²²³ J. D. Loudon and G. Tennant, *J. Chem. Soc.* p. 4268 (1963).

²²⁴ R. B. Davis and L. C. Pizzini; *J. Org. Chem.* **25**, 1884 (1960). R. B. Davis (University of Notre Dame), U.S. Patent 3,156,704; *Chem. Abstr.* **62**, 2743 (1965).

²²⁵ G. N. Walker, *J. Org. Chem.* **27**, 1929 (1962).

p-Nitrotoluene and *p*-nitroanisole do not give anthranils. Simple displacement of the halogen atom has been reported when the reaction is carried out in pyridine.²²⁶

o-Chloronitrobenzene undergoes a normal nucleophilic displacement of the halogen atom using diethyl sodiomalonate or ethyl sodio-cyanoacetate. The product (**106**, R=COOEt or CN) partly decomposes to ethyl anthroxanate (**107**, R=COOEt) or 3-cyanoanthranil (**107**, R=CN) (the latter only in small yield) on distillation.²²⁷



3. Formation from Other Heterocycles

N-Hydroxyisatin (**108**) isomerizes in dilute sodium hydroxide solution to anthroxanic acid,^{228, 229} and its monooxime (**109**) gives the same product on heating with hydrochloric acid.²³⁰ The rearrangement also takes place in sodium carbonate^{229, 231} and ammonia²²⁹ solutions; in the last case the amide is formed. It is probable that *N*-hydroxyisatin, or trihydroxyindole, is an intermediate in other rearrangements leading to anthroxanic acid.¹⁵⁶⁻¹⁵⁸



²²⁶ H. Neresheimer and W. Ruppel, U.S. Patent 2,080,057; German Patent 603,622 (1934); *Chem. Abstr.* **29**, 817 (1935).

²²⁷ C. A. Grob and O. Weissbach, *Helv. Chim. Acta* **44**, 1748 (1961).

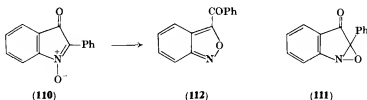
²²⁸ G. Heller, *Ber. Deut. Chem. Ges.* **42**, 470 (1909).

²²⁹ F. Arndt, B. Eistert, and W. Partale, *Ber. Deut. Chem. Ges.* **60**, 1364 (1927).

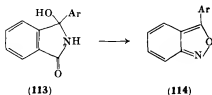
²³⁰ A. Reissert, *Ber. Deut. Chem. Ges.* **41**, 3921 (1908).

²³¹ L. Alessandri, *Gazz. Chim. Ital.* **57**, 195 (1927).

2-Phenylisatogen (**110**) rearranges in methanolic sulfuric acid to an isomeric compound, which was called 2-phenylisoisatogen and formulated as **111**.²³² Recent work has shown, however, that the product is 3-benzoylanthranil (**112**), formed by hydrolysis and recyclization of the isatogen.²³³⁻²³⁶



Certain benzophenone-2-carboxamides exist as the cyclic structures **113**, and Hofmann degradation of these compounds does not form the amines, but rather what are probably anthranils (**114**).²³⁷



4-Acetylbenzofuroxan (**115** \rightleftharpoons **116**) is the suggested intermediate in the conversion by heat of 3-azido-2-nitroacetophenone (**117**) into 3-methyl-7-nitroanthranil (**118**).²³⁸

A unique method of anthranil (**119**) formation, making bonds 5—6 and 7—7a and building up the homocyclic ring, occurs in polyphosphoric acid as the result of a series of reactions starting from the oxime

²³² P. Ruggli, E. Caspar, and B. Hegedüs, *Helv. Chim. Acta* **22**, 140 (1939).

²³³ M. Sundaralingam, *Dissertation Abstr.* **23**, 843 (1962); *Chem. Abstr.* **58**, 6274 (1963).

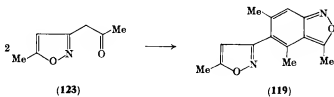
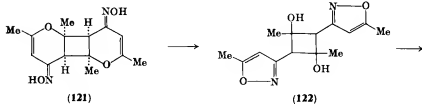
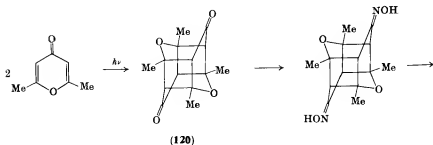
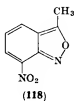
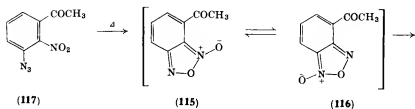
²³⁴ M. Sundaralingam and G. A. Jeffrey, *Acta Cryst.* **15**, 1035 (1962); *Chem. Abstr.* **58**, 96 (1963).

²³⁵ J. L. Pinkus, T. Cohen, M. Sundaralingam, and G. A. Jeffrey, *Proc. Chem. Soc.* p. 70 (1960).

²³⁶ J. L. Pinkus, G. G. Woodyard, and T. Cohen, *J. Org. Chem.* **30**, 1104 (1965).

²³⁷ W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta* **42**, 1085 (1959).

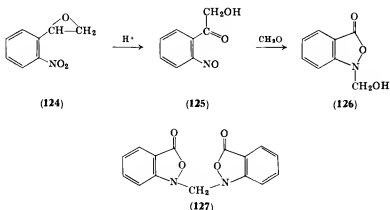
²³⁸ A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *Angew. Chem.* **76**, 816 (1964); *Angew. Chem. Intern. Ed. English* **3**, 693 (1964).



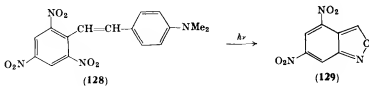
of a photodimer (120) of 2,6-dimethyl-4-pyrone.²³⁹ The intermediate compounds (121–123) were all isolated.

4. Other Methods

a. *From o-Nitrobenzaldehyde and Diazomethane.* *o*-Nitrobenzaldehyde reacts with diazomethane to form nitraldine (124),^{240, 241} which is transformed by dilute acids into the isomeric nitroso compound (125). 125 readily rearranges further, and in the presence of formaldehyde gives 1-hydroxymethyl-2,1-benzisoxazolin-3-one (126); without added formaldehyde 127 is formed. Nitraldine was also reported to form some anthranil on reduction.²⁴¹



b. *Photochemical Methods.* *o*-Nitrostilbenes undergo rearrangement to isotogens in ultraviolet light; compound 128 gives in addition a little 4,6-dinitroanthranil (129).²⁴²



²³⁹ P. Yates and E. S. Hand, *Tetrahedron Letters* p. 669 (1961).

²⁴⁰ F. Arndt and W. Partale, *Ber. Deut. Chem. Ges.* **60**, 446 (1927).

²⁴¹ F. Arndt, B. Eistert, and W. Partale, *Ber. Deut. Chem. Ges.* **61B**, 1107(1928).

²⁴² J. S. Splitter and M. Calvin, *J. Org. Chem.* **20**, 1086 (1955).

B. PHYSICAL PROPERTIES AND STRUCTURE

Anthranil and its 3-methyl compound are colorless oily liquids with a characteristic smell. Other derivatives so far reported are colorless or yellow crystalline solids; ca. 240 are listed in tables XII–XVIII at the end of this chapter, with their melting or boiling points. They show very weakly basic character, being soluble in concentrated mineral acids, but precipitated on dilution (see Section IV).

The structure of anthranil has been the subject of a large number of publications. The history of the controversy is briefly outlined by Speroni.⁵⁸ Friedländer¹⁰⁹ in 1882 first regarded it as the anhydride of anthranilic acid, and ascribed to it lactam (130) or lactim (131) formulas, but the tricyclic structure (132) was suggested in the following year.^{183, 243} There followed a period of vigorous and often polemical discussion, with the lactam structure being supported principally by Heller,^{133, 244–248} while Bamberger^{121, 249, 250} favored formula 132. The existence of acyl derivatives, which were at that time represented by 133, appeared to support 130, but in favor of 132



(130)



(131)



(132)



(133)



(134)



(135)



(136)

was the formation of methyl and carboxy derivatives (134), by routes analogous to those for the parent, from starting materials in which the substituent was undoubtedly attached to carbon. Heller later

²⁴³ P. Friedländer and S. Wleügel, *Ber. Deut. Chem. Ges.* **16**, 2227 (1883).

²⁴⁴ G. Heller and G. Fieselmann, *Ann. Chem.* **324**, 118 (1902).

²⁴⁵ G. Heller, *Ber. Deut. Chem. Ges.* **36**, 2762 (1903).

²⁴⁶ G. Heller, *Ber. Deut. Chem. Ges.* **36**, 4178 (1903).

²⁴⁷ G. Heller, *J. Prakt. Chem.* [2] **70**, 516 (1905).

²⁴⁸ G. Heller, *Ber. Kgl. Sächs. Ges. Wiss., Math.-Phys. Kl.* **62**, 51 (1910); *Chem. Zentr.* II, 975 (1910).

²⁴⁹ E. Bamberger, *Ber. Deut. Chem. Ges.* **37**, 966 (1904).

²⁵⁰ E. Bamberger, *Ber. Deut. Chem. Ges.* **42**, 1647 (1909).

suggested a tautomerism between **130** and **132**,^{143, 247} but obtained no support for this.

In a later paper of Bamberger, he claimed that structure **132** did not represent a tricyclic ring system, but should be regarded as equivalent to Angeli's bicyclic formula (**135**), and that anthranil contained an isoxazole ring.²⁵⁰ However, he continued to use **132** in his publications, clearly wishing to avoid the apparent *o*-quinonoid structure **135** contains. (One may still sometimes find the tricyclic formulation used, no doubt for the same reason.) Somewhat later, chemical means were used to distinguish between the bi- and tricyclic systems, and some (negative) evidence was obtained in favor of the former. In **132**, C-3 is asymmetric, and if anthranil is correctly represented by this structure it should be capable of resolution into optical antipodes. However, attempts to resolve anthroxanic acid by means of its salts with alkalis gave no positive result.²⁵²

A further (nitron) formula (**136**) was proposed by Staudinger in 1919,²⁵³ but quickly disposed of by Bamberger.¹⁶⁷ More recently, some Soviet authors^{141, 254} have revived it, on rather ambiguous chemical grounds.

The structural problem was finally cleared up by physical methods, including molar refraction,²⁵⁵⁻²⁶² and ultraviolet²⁶³ and Raman²⁶⁴ spectroscopy. The 3-benzoyl derivative has also been submitted to X-ray analysis.²³³⁻²³⁵ All the evidence supports a planar fused system of six- and five-membered rings, although some of the earlier work was interpreted in terms of other structures. The proton NMR spectrum of anthranil has been analyzed;²⁶⁵ the parameters are listed in Table A.

²⁵¹ G. Heller, *Ber. Deut. Chem. Ges.* **49**, 523 (1916).

²⁵² H. Leuchs, *Ber. Deut. Chem. Ges.* **58**, 1452 (1925).

²⁵³ H. Staudinger and K. Miescher, *Helv. Chim. Acta* **2**, 555 (1919).

²⁵⁴ M. N. Shchukina and G. S. Predvoditeleva, *Dokl. Akad. Nauk SSSR* **110**, 230 (1956); *Chem. Abstr.* **51**, 4996 (1957).

²⁵⁵ R. Anschütz and O. Schmidt, *Ber. Deut. Chem. Ges.* **35**, 3470 (1902).

²⁵⁶ O. Schmidt, *Ber. Deut. Chem. Ges.* **36**, 2459 (1903).

²⁵⁷ J. W. Brühl, *Ber. Deut. Chem. Ges.* **36**, 3634 (1903).

²⁵⁸ J. W. Brühl, *Ber. Deut. Chem. Ges.* **36**, 4294 (1903).

²⁵⁹ O. Schmidt, *Ber. Deut. Chem. Ges.* **38**, 200 (1905).

²⁶⁰ J. W. Brühl, *Z. Physik. Chem.* **59**, 507 (1907).

²⁶¹ O. Schmidt, *Z. Physik. Chem.* **58**, 513 (1907).

²⁶² K. von Auwers, *Ann. Chem.* **437**, 63 (1924).

²⁶³ J. Scheiber, *Ber. Deut. Chem. Ges.* **44**, 2409 (1911).

²⁶⁴ K. W. F. Kohlrausch and R. Seka, *Ber. Deut. Chem. Ges.* **71B**, 1563 (1938).

²⁶⁵ B. Ternai, unpublished work (1965).

Other NMR data on substituted anthranils are available.^{135,239}

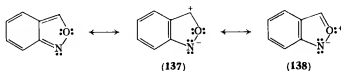
The ultraviolet spectra of some anthranils have been reported;^{135, 178,239, 263, 266} that of anthranil is reproduced in Ref. 266. Infrared data on some 3-keto compounds have been presented.^{236, 267}

TABLE A
NMR PARAMETERS FOR ANTHRANIL^a

H atom	τ (ppm)	J (cps)	J (cps)
3	0.60	3,4 -0.05	4,6 0.99
4	2.47	3,5 0.04	4,7 0.93
5	3.08	3,6 -0.04	5,6 6.72
6	2.76	3,7 1.09	5,7 0.76
7	2.335	4,5 8.66	6,7 8.70

^a Error ± 0.02 cps. Spectra were taken at both 40 and 60 Mc/s, of a sample containing tetramethylsilane, without solvent.

Anthranil may be regarded as a heteroaromatic 10- π -electron system. Its dipole moment (3.06 D)⁵⁹ indicates a considerable degree



of polarity, which may be attributed to contributions from canonical forms such as **137** and **138** to the ground state of the molecule.

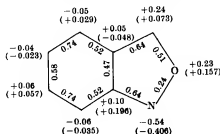


Fig. 2. π -Electron densities and mobile bond orders for anthranil.⁶⁰ Density values in parentheses are taken from Berthier and Del Re.⁶¹

²⁶⁶ P. Ramart-Lucas and M. Grumez, *Bull. Soc. Chim. France* [5] **17**, 317 (1950).

²⁶⁷ R. A. Abramovitch, *Proc. Chem. Soc.* p. 8 (1957).

Hückel molecular orbital calculations have been performed for anthranil; the π electron densities and mobile bond orders of Del Re⁶⁰ and Berthier and Del Re⁶¹ are given in Fig. 2.

C. CHEMICAL PROPERTIES

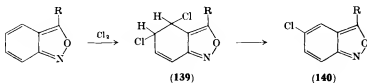
1. Salts and Adducts

Simple salts of anthranils have so far not been described in the literature, but their solubility in mineral acids, and ultraviolet spectral data of solutions in hydrochloric acid of various strengths,²⁶³ provide evidence for protonation. Quaternary salts have not been isolated. Anthranil itself forms a picrate²⁶⁸ and a hexachlorostannate.²⁴⁶ Compounds in this series are very prone to form crystalline complexes with mercuric chloride, which are useful for their isolation and characterization. Such adducts are particularly well-known for the parent^{109, 187, 268} and the 3-methyl^{121, 122, 137} compound, but they are also known for 3-aryl derivatives^{122, 128, 176, 194, 196} and others.¹⁸²

6-Nitroanthranils form addition compounds of unknown structure with hydrazine.^{179, 180, 182}

2. Electrophilic Substitution

a. *Halogenation.* The action of chlorine on anthranil²⁶⁹ or its 3-methyl derivative¹²² in cold hydrochloric acid first gives an addition product (139)¹³⁵ which is reduced by aqueous iodide ion to the starting anthranil,¹²² and which with dilute base or on steam-distillation splits out hydrogen chloride to form the 5-substituted product (140).²⁷⁰ Sodium nitrite in concentrated hydrochloric acid also converts 4-methylantranil into its chlorine addition product, amongst other things.^{120, 122} Bromination of anthranil gives 5-bromoanthranil analogously.^{269, 270}



²⁶⁸ Y. Iskander and Y. Riad, *J. Chem. Soc.* p. 2054 (1951).

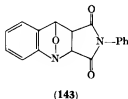
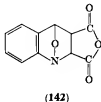
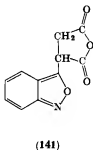
²⁶⁹ E. Bamberger and J. Lublin, *Ber. Deut. Chem. Ges.* **42**, 1676 (1909).

²⁷⁰ K.-H. Wünsch, H. Linke, A. J. Boulton, and Altaf-ur-Rahman, *Chem. Commun.* p. 408 (1965).

b. *Nitration*. Potassium nitrate in concentrated sulfuric acid converts 3-methylanthranil into its 5-nitro derivative. The parent compound gives mainly 5- but also a little 7-substitution product, under the same conditions.^{135, 270}

3. Diels-Alder Reactions

Two examples of diene addition products have been claimed in the literature. Structures **141** and **142** were considered for a 1:1 adduct of anthranil and maleic anhydride, and since 3-phenylanthranil did not react analogously, structure **141** was preferred.²⁷¹ Also, anthranil and *N*-phenylmaleimide have been reported to give compound **143**, which with alkali is hydrolyzed and dehydrated to give acridinic acid.²⁷² Attempts to form Diels-Alder adducts between 3-benzoylanthranil and maleic anhydride or *n*-butyl vinyl ether met with no success.¹⁶⁵



4. Ring Fission

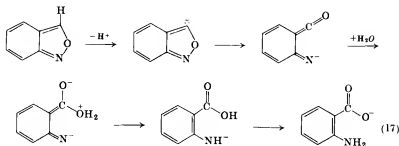
The readiness with which the anthranil ring is opened is a particular feature of reactions in this series. The fission takes place with a wide variety of reagents and leads to many different products.

a. *With bases*. Anthranil is converted by dilute sodium hydroxide^{109, 243} or aqueous ammonia¹⁰⁹ into anthranilic acid, and similar behavior is typical of other anthranils unsubstituted in the 3-position.^{180, 270} The following reaction pathway [Eq. (17)], initiated by deprotonation by the base, is plausible.⁶⁰

Reaction of anthranil with hydroxylamine leads to a wide variety of compounds, which all arise via the initially formed *o*-hydroxylamino-

²⁷¹ A. Schönberg and A. Mostafa, *J. Chem. Soc.* p. 654 (1943).

²⁷² C. D. Nenitzescu, E. Ciorănescu, and L. Birlădeanu, *Comun. Acad. Rep. Populare Romîne* **8**, 775 (1958); *Chem. Abstr.* **53**, 18003 (1959).



benzaldoxime. Chief amongst them are *o*-amino-, *o*-nitro-, *o*-azoxy-, and, in the presence of air, *o*-azidobenzaldoxime.²⁷³⁻²⁷⁶ Primary aromatic amines,^{276, 277} and hydrazine and its derivatives,^{121, 246, 251, 274} give products of undetermined structure.

3-Methylantranil is much more stable towards bases than the unsubstituted compound. However, prolonged heating with sodium hydroxide was reported to form 2-aminoacetophenone,²⁵⁰ and the action of hydroxylamine on a derivative produced a mixture of the corresponding aminoacetophenone and its oxime.¹²⁵

b. *With Dimethyl Sulfate.* This reagent converts anthranil into a mixture of *o*-aminobenzaldehyde and its mono- and di-*N*-methyl derivatives.^{246, 249}

c. *By Reduction.* The isoxazole ring of anthranils can be opened by reduction, when *o*-aminoketo compounds (144) are usually formed. The following reducing agents have brought about this reaction: iron^{124, 224, 278} or zinc²²² and acetic acid; zinc and hydrochloric acid,^{178, 222} calcium chloride,^{196, 279} or ammonium chloride,^{214, 215, 217} tin or stannous chloride and hydrochloric acid;^{120, 123, 131, 219} ferrous sulfate and ammonia;^{110, 163} sodium dithionite;²²¹ hydrogen with platinum^{128, 132} or palladium.²²⁵ In some cases further reduction was

²⁷³ A. Einhorn, *Ann. Chem.* **295**, 187 (1897).

²⁷⁴ O. Buhlmann and A. Einhorn, *Ber. Deut. Chem. Ges.* **34**, 3788 (1901).

²⁷⁵ E. Bamberger and E. Demuth, *Ber. Deut. Chem. Ges.* **34**, 4015 (1901).

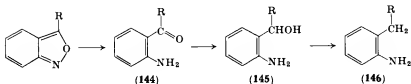
²⁷⁶ E. Bamberger, *Ber. Deut. Chem. Ges.* **35**, 3893 (1902).

²⁷⁷ G. Heller and E. Grinthal, *Ber. Kgl. Sächs. Ges. Wiss., Math.-Phys. Kl.* **62**, 46 (1910); *Chem. Abstr.* **5**, 2818 (1911).

²⁷⁸ J. C. E. Simpson and O. Stephenson, *J. Chem. Soc.* p. 353 (1942).

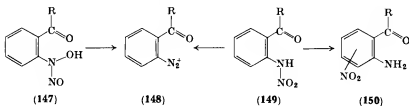
²⁷⁹ I. Tănăsescu and A. Silberg, *Bull. Soc. Chim. France* [5] **3**, 2383 (1936); I. Tănăsescu, C. Anghel, and A. Popescu, *Studia Univ. Babes-Bolyai, Ser. Chem.* **8**, 141 (1963); *Chem. Abstr.* **61**, 13279 (1964).

observed, the keto group forming a hydroxymethylene (145) (HI²¹⁹) or methylene (146) (H₂/Raney Ni,¹²⁸ H₂/Pd/C,²¹⁹ HI²²⁰) group.



d. *By Oxidation.* Anthranil is oxidized by potassium dichromate and sulfuric^{171,180} or nitric¹³³ acid to *o*-azoxybenzoic acid, and by potassium permanganate to *o*-nitroso- or *o*-nitrobenzaldehyde.²⁸⁰ The 3-methyl derivative forms *o*-nitrosoacetophenone with acid dichromate.¹³³

e. *With Nitrous Acid.* Anthranil is very readily cleaved with nitrous acid. With sodium nitrite and 23% hydrochloric acid the first isolable product is the nitrosohydroxylamine (147), which becomes reduced to the diazonium salt (148), detected by its coupling with β -naphthol.^{269,280} *o*-Nitrosobenzaldehyde was also isolated from the reaction.²⁸⁰ Diazonium salts have also been observed in the reaction with 3-methyl, 3-formyl, 3-carboxy, and a number of 3-aryl derivatives^{122,269,281} (in the last case, acridones are the chief products; see the following section). Anthranil and 3-methylantranil give in addition (and in the latter case predominantly) the nitramines (149), which may rearrange to give a nitroaniline (150), or become reduced to the diazonium salt.²⁸²



Sodium nitrite and 39% hydrochloric acid give chlorinated products, probably arising from chlorine in the reaction mixture, in addition to those formed as above.^{120,122,269}

²⁸⁰ E. Bamberger and A. Fodor, *Ber. Deut. Chem. Ges.* **43**, 3321 (1910).

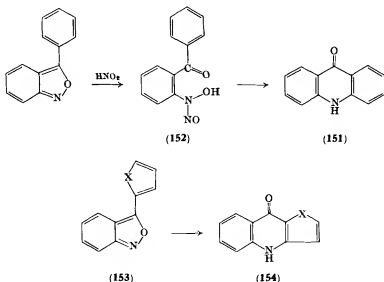
²⁸¹ E. Bamberger, *Ber. Deut. Chem. Ges.* **42**, 1707 (1909).

²⁸² E. Bamberger, *Ber. Deut. Chem. Ges.* **48**, 537 (1915).

5-Nitrosalicylaldehyde can be isolated after "diazotization" of anthranil, followed by heating.²⁶⁸

5. Rearrangements into Other Heterocycles

a. *Acridones*. The rearrangement of 3-arylanthranils into acridones (**151**) is one of considerable importance. It takes place very readily in the presence of nitrous acid, and the nitrosohydroxylamine (**152**) has been suggested to be an intermediate.^{195,197,198,279,281} The reaction of fuming nitric acid with 3-phenylanthranil also gives acridone,



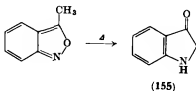
which is nitrated in the process.²⁸³ Acridones are often formed during the preparation of 3-arylanthranils (Section III, A, 1, j), particularly when 2,4-dinitrobenzaldehyde is used as a starting material, when nitrous acid may be formed by decomposition,¹⁷⁶ or when a little nitrite is added to the reaction mixture.^{199,284} *N*-Hydroxyacridones are also produced as by-products in the rearrangement reaction;^{195,197-199,206,283} these compounds were at first thought by

²⁸³ A. Kliegl and A. Fehrle, *Ber. Deut. Chem. Ges.* **47**, 1631 (1914).

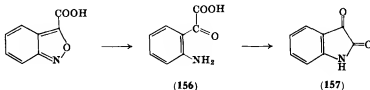
²⁸⁴ K. Lehmstedt, *Ber. Deut. Chem. Ges.* **65**, 999 (1932); German Patent 581,328; *Chem. Abstr.* **27**, 5083 (1933).

Tănăsescu to be anthranil-*N*-oxides.^{201, 206, 213, 285} Nitrous acid treatment of other 3-arylanthranils (**154**, X = O, S) gives, analogously, the furano-¹³⁰ and thieno-¹²⁹ quinolones (**154**, X = O, S, respectively).

b. *Indole Derivatives*. 3-Methylanthranil rearranges on strong heating to form indoxyl (**155**); in the presence of air, indigo is formed.^{120, 122} Analogous reactions have been described for a bromo-substituted compound.²⁸⁶



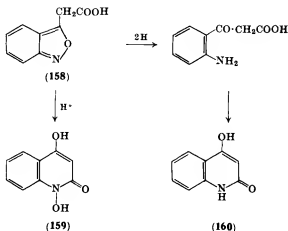
Anthroxanic acid can be reduced ($\text{FeSO}_4/\text{NH}_3$) to isatic acid (**156**), which then recyclizes to isatin (**157**).^{159, 183} 3-Acyldanthranils on reduction (Zn/HOAc or $\text{H}_2/\text{Raney Ni}$) form indoxyls, also by recyclization.²³⁶



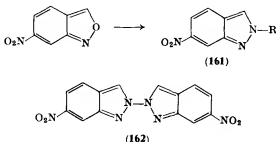
c. *Quinoline Derivatives*. Although anthranils as a rule are reasonably stable towards acids, the 3-acetic acid derivative (homoanthroxanic acid, **158**) fairly easily rearranges with warm 10% hydrochloric acid into 1,4-dihydroxycarbostyryl (**159**). This rearrangement was discovered by Heller and Tischner,¹⁶³ who assigned an incorrect structure to the product, which was later rectified by Arndt *et al.*¹⁶⁴ The latter authors, however, argued that, since anthranils are generally unaffected by acids, **158** was unlikely to be the correct structure of the starting material. The situation has only recently been resolved, and structure **158** confirmed.¹⁶⁵ Reduction of the anthranil leads to ring opening and recyclization, forming 4-hydroxycarbostyryl (**160**).¹⁶³

²⁸⁵ I. Tănăsescu and E. Ramontianu, *Bull. Soc. Chim. France* [5] **1**, 547 (1934).

²⁸⁶ W. J. Bruining, *Rec. Trav. Chim.* **41**, 671 (1922).



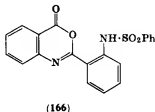
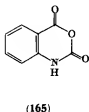
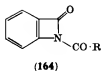
d. *Indazole Derivatives.* 6-Nitroanthranil is converted by amines into an interesting range of compounds, to which 2-indazole structures have been assigned. Thus, aniline and phenylhydrazine form **161**, ($R = Ph$) and **161**, ($R = NHPh$), respectively. Hydrazine itself gives the 2,2-diindazolyl (**162**).¹⁸¹



e. *3,1-Benzoxazine Derivatives; "Acylantranils."* Anthranils with an unsubstituted 3-position react with acid chlorides^{121,243,287} and anhydrides^{109,116,121,179,255} to give 3,1-benzoxazin-4-ones (**163**), to which at first different structures (**164**) and the name "acylantranils" were ascribed. The same ring system is formed with anthranil and *N*-phenylbenzimidoyl chloride.²⁸⁸ Chloroformic ester gives isatoic

²⁸⁷ I. R. Gambhir and S. S. Joshi, *J. Indian Chem. Soc.* **41**, 47 (1964).

²⁸⁸ O. Mumm and H. Hesse, *Ber. Deut. Chem. Ges.* **43**, 2508 (1910).



anhydride (165) in a similar way.^{121, 243, 289} Benzene sulfonyl chloride forms **166**, using two molecules of anthranil.^{246, 290}

The so-called "acylanthranils" played an important role in the discussion on the structure of anthranils. Heller regarded the possibility of obtaining them by acylation of anthranils as evidence for structure **164**, and for the lactam structure for anthranils in general. However, he was soon forced to reconsider this view. In particular, it was realized that the product from ethyl chloroformate and anthranil was not anthranil carboxylic ester,²⁴³ but rather the known compound isatoic anhydride (165).^{117, 121, 289, 291-293} Isatoic anhydride and benzoyl chloride formed "benzoylanthranil,"^{291, 294} and the structural connection between the two compounds was recognized. Nevertheless, structure **163**, (R = Ph), first suggested by Angeli,²⁹⁵ and undoubtedly correct, has been too often overlooked, and some later authors, even up to the present day, have persisted with the lactam formula.²⁹⁶⁻³⁰¹

²⁸⁹ E. Erdmann, *Ber. Deut. Chem. Ges.* **32**, 2158 (1899).

²⁹⁰ G. Schroeter, *Ber. Deut. Chem. Ges.* **40**, 2628 (1907).

²⁹¹ E. von Meyer, *J. Prakt. Chem.* [2] **30**, 484 (1884).

²⁹² S. Niewentowski and B. Rosański, *Ber. Deut. Chem. Ges.* **22**, 1672 (1889).

²⁹³ C. Graebe and S. Rostovzeff, *Ber. Deut. Chem. Ges.* **35**, 2747 (1902).

²⁹⁴ E. von Meyer and T. Bellmann, *J. Prakt. Chem.* [2] **33**, 18 (1886).

²⁹⁵ A. Angeli and F. Angelico, *Gazz. Chim. Ital.* **30** II, 268 (1900).

²⁹⁶ P. Karrer, G. H. Diechmann, and W. T. Haebler, *Helv. Chim. Acta* **7**, 1031 (1929).

²⁹⁷ L. Elion, *Rec. Trav. Chim.* **44**, 1106 (1925).

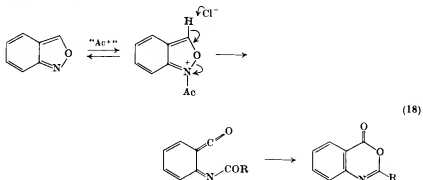
²⁹⁸ O. G. Backeberg, *J. Chem. Soc.* p. 390 (1933).

²⁹⁹ A. Corbellini, C. Botrugno, and P. Villa, *Gazz. Chim. Ital.* **66**, 186 (1936).

³⁰⁰ E. B. Wornack, H. Campbell, and G. B. Dodds, *J. Chem. Soc.* p. 1402 (1938).

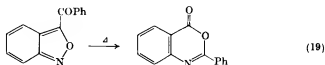
³⁰¹ P. R. Levy and H. Stephen, *J. Chem. Soc.* p. 985 (1956).

The following mechanism [Eq. (18)], largely after Mumm and Hesse,²⁸⁸ may serve to explain the formation of these compounds from anthranils.



Although it is not possible to make anthranils directly from anthranilic acids, "acylanthranils" are particularly easily obtained from them, using acid anhydrides,^{252,297} acid chlorides,²⁴⁴ or *N*-phenylbenzimidoyl chloride,^{288,301} or by the action of a variety of dehydrating agents on acylanthranilic acids.^{255,295,299,302,303} The formation of "acetylanthranil" from *o*-nitrophenylacetic acid and acetic anhydride probably goes via anthranil derivatives.³⁰⁴

While the "acylanthranils" belong to another ring system, examples of 3-acyl-substituted anthranils are known (Section III, C, 6, a); one of them (3-benzoylanthranil) rearranges on heating into the isomeric 2-phenyl-3,1-benzoxazin-4-one [Eq. (19)].¹⁶⁵



6. Properties and Reactions of the Functional Groups

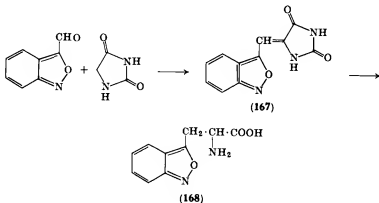
a. *Keto Groups.* The 3-aldehyde forms a bisulfite adduct,¹⁸³ an anil,¹⁸³ and an oxime,¹⁶³ in the normal way, and can be oxidized with

³⁰² E. Mohr and F. Kohler, *Ber. Deut. Chem. Ges.* **40**, 997 (1907); G. Heller, *ibid.* **48**, 1106 (1925).

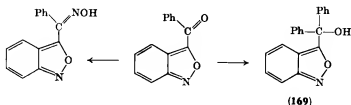
³⁰³ P. Ruggli and W. Leonhardt, *Helv. Chim. Acta* **7**, 898 (1924).

³⁰⁴ G. N. Walker, *J. Am. Chem. Soc.* **77**, 6698 (1955).

potassium permanganate to the acid.¹⁸³ It condenses with hydantoin in the presence of piperidine to give **167**, which on heating with ammonium sulfide in a sealed tube forms β -(anthranil-3-yl)alanine (**168**).³⁰⁵



Ruggli's "isoisatogens," formulated originally as **111**,^{232, 306-308} are now known to be 3-acylanthranils.²³³⁻²³⁶ 3-Benzoylanthranil forms an oxime, and with phenyl magnesium bromide gives **169**.^{235, 236}



b. *Carboxy Groups.* Anthroxanic acid forms salts with metal cations¹⁴³ and with organic bases,²⁵² as might be expected. Phosphorus pentachloride gives the acid chloride.^{164, 178, 236} Esters may be obtained from the acid by esterification,^{143, 227} and amides from the esters or the acid chloride.^{160, 178} Esters and amides have also been

³⁰⁵ G. S. D'Alcontres and G. Cuzzocrea, *Atti Soc. Peloritana Sci. Fis. Mat. Nat.* **3**, 179 (1956/57); *Chem. Abstr.* **52**, 1994 (1958).

³⁰⁶ P. Ruggli, *Ber. Deut. Chem. Ges.* **52**, 1 (1919); P. Ruggli and A. Bolliger, *Helv. Chim. Acta* **4**, 626 and 637 (1921); P. Ruggli, A. Bolliger, and W. Leonhardt, *ibid.* **6**, 594 (1923); P. Ruggli and H. Zaeslin, *ibid.* **22**, 134 (1939).

³⁰⁷ P. Ruggli and H. Cuenin, *Helv. Chim. Acta* **27**, 649 (1944).

³⁰⁸ G. Heller and W. Boessneck, *Ber. Deut. Chem. Ges.* **55**, 475 (1922).

made by direct ring synthesis.^{143,178,227} The nitrile is hydrolyzed to the acid normally.²²⁷ The acid chloride reacts with diazomethane to give the diazoketone, which forms the 3-chloroacetyl derivative with hydrochloric acid, but would not undergo a Wolff rearrangement to the homologous acid.¹⁶⁴ Decarboxylation of anthroxanic acid was long thought to be impossible,^{133,183,309} until Bamberger succeeded in isolating a small amount of anthranil from the reaction.³¹⁰ Homanthroxanic acid, on the other hand, is decarboxylated without difficulty, giving 3-methylanthranil.¹⁶³ The carboxy group of the latter acid activates the adjacent methylene group, so that anthroxan-aldehyde oxime is formed with nitrous acid.¹⁶³

Carboxy groups in the homocyclic ring show normal properties;¹¹⁵ the pK value of one compound has been determined.³¹¹

c. *Hydroxy Groups*. A hydroxy group in the 3-position produces a system tautomeric with the 2,1-benzisoxazolin-3-ones, and it is under this heading (Section III, E) that these compounds are considered.

Hydroxy groups in the benzene ring have been acylated,¹¹⁶ and those in a phenyl substituent methylated.²⁷⁸

d. *Nitro Groups*. 6-Nitro-3-phenylanthranil may be reduced with stannous chloride and hydrochloric acid to the amino compound.¹⁹⁶

e. *Amino Groups*. 3-Aminoanthranil has recently been prepared, and has been found to contain an amino group (170) rather than the tautomeric imino structure (171).¹⁵⁰



(170)



(171)

Amino groups in phenyl substituents form acyl²¹⁴ and benzyldene^{214,216,217} derivatives; the latter are cleaved by hydrochloric acid^{214,215,217} and hydrazine.²¹⁴ The amino group may be replaced by a chlorine atom in a Sandmeyer reaction;²⁷⁹ apparently here (in 3-*p*-aminophenylanthranil), nitrous acid does not affect the usual rearrangement to acridones.

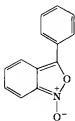
³⁰⁹ G. Heller, *J. Prakt. Chem.* [2] **80**, 320 (1909).

³¹⁰ E. Bamberger, *J. Prakt. Chem.* [2] **81**, 254 (1910).

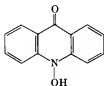
³¹¹ J. Tirouflet, *Compt. Rend.* **236**, 1426 (1953).

D. ANTHRANIL-*N*-OXIDES

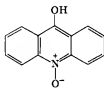
For some time Tanasescu held the view that a group of compounds obtained by reaction of *o*-nitrobenzaldehydes with aromatic compounds in concentrated sulfuric acid, containing one oxygen atom more than the arylanthranils formed concurrently, were anthranil-*N*-oxides (e.g., **172**).^{200,201,206} Lehmstedt opposed this, and put forward the *N*-hydroxyacridone structure (**173**),^{213,312} which Tanasescu himself later adopted, although he preferred the tautomeric hydroxyacridine-*N*-oxide structure (**174**).^{195,198,199,313}



(172)



(173)



(174)

Tanasescu's proposed "tautomerism" of *o*-nitrobenzaldehyde (to **175** or **176**), photochemically,^{202-205, 207, 285} and of nitraldine (to **177**),³¹⁴ was also heavily attacked from all sides,²⁰⁸⁻²¹³ and must be considered as erroneous. Analogous *N*-oxides have also featured in other photochemical rearrangements.³¹⁵



(175)



(176)



(177)

The reaction between *o*-nitrobenzoic acid and benzene in the presence of trifluoroacetic anhydride and boron trifluoride has been

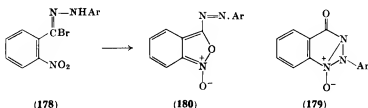
³¹² K. Lehmstedt, *Ber. Deut. Chem. Ges.* **65**, 834 (1932).

³¹³ I. Tănăsescu and Z. Frenkel, *Acad. Rep. Populare Romine, Studii Cercetari Chim.* **4**, 227 (1956); *Chem. Abstr.* **51**, 10527 (1957).

³¹⁴ I. Tănăsescu, *Bull. Soc. Chim. France* [4] **43**, 1264 (1928).

³¹⁵ W. Ried and M. Wilk, *Ann. Chem.* **590**, 91 and 111 (1954).

reported by Szmant and Harmuth³¹⁶ to give a white by-product, m.p. 187–188°, along with the expected *o*-nitrobenzophenone. It could be converted by nitrite and sulfuric acid into acridone, and by iron and acetic acid into *o*-aminobenzophenone. These, and analytical data, led the authors to propose the 3-phenylanthranil-1-oxide structure (172) for the compound. A second example was claimed by Gibson,^{317, 318} who re-examined earlier work by Chattaway³¹⁹ on the action of alkali upon α -bromo-*o*-nitrobenzaldehyde arylhydrazones (178). The original authors had proposed bridged-ring structures (179) for the explosive products of the reaction, but ultraviolet and infrared spectral evidence, and a simpler mechanism of formation, were invoked^{317, 318} in favor of the anthranil-*N*-oxide formula (180, Ar = 2,4-dibromophenyl).



Although the possibility of anthranil-*N*-oxide formation may be recognized, there are certain difficulties in the way of accepting at least one of the foregoing examples. The two generalized systems (181 and 182) differ, in certain conformations, only in their electron distribution, and interconversion would be expected to occur so readily as to preclude isolation of other than the energetically more stable form. Several examples may be cited to bear this out. Thus, 2-phenyl-benzotriazole-1-oxide (181, X = N, Y = NPh) is well-known,³²⁰ but no evidence for the independent existence of *o*-nitrosoazobenzene (182, X = N, Y = NPh) is available. The rapid tautomerism of benzofuroxan (181, X = N, Y = O) from the 1- to the 3-oxide structure, through

³¹⁶ H. H. Szmant and C. M. Harmuth, *J. Am. Chem. Soc.* **81**, 962 (1959).

³¹⁷ M. S. Gibson, *Nature* **193**, 474 (1962).

³¹⁸ M. S. Gibson, *Tetrahedron* **18**, 1377 (1962).

³¹⁹ The work of F. D. Chattaway *et al.* has been reviewed by J. G. Erickson in "The Chemistry of Heterocyclic Compounds", (A. Weissberger, ed.), Vol. 10, p. 27. Wiley (Interscience) New York, 1956.

³²⁰ A. Werner and E. Stiasny, *Ber. Deut. Chem. Ges.* **32**, 3256 (1892).

o-dinitrosobenzene (**182**, $X=N$, $Y=O$),³²¹ implies that the energy barrier between the two is not large compared with the energy difference. The same may be said for *o*-nitronitrosobenzene (**182**, $X=N^+-O^-$, $Y=O$), although here the equilibrium lies to the right, and the isomerization of substituted compounds of this type³²² is the only evidence for the transitory existence of **181** ($X=N^+-O^-$, $Y=O$). Other instances could be quoted.



(181)



(182)

In the case of the anthranil-*N*-oxides (**181**, $X=CR$, $Y=O$), however, several examples of the isomeric *o*-nitrosobenzoyl compounds are known in the literature, viz., *o*-nitrosobenzaldehyde (**182**, $X=CH$, $Y=O$),^{280, 323} *o*-nitrosoacetophenone (**182**, $X=CMe$, $Y=O$),¹³³ and *o*-nitrosobenzophenone (**182**, $X=CPh$, $Y=O$).¹⁵⁶ They are described as almost colorless solids which give green solutions, and in this behave as typical nitroso compounds. The last-named compound (m.p. 129–130°) is clearly different from the 3-phenylanthranil-1-oxide³¹⁶ described above, and it is the present authors' opinion that only one can be correct.

E. 2,1-BENZISOXAZOLIN-3-ONES

The formation of these compounds has already been dealt with (Section III, A). No firm evidence is available to indicate whether oxo (**183**) or hydroxy (**184**) structures are favored in this series. In the case of 4-substituted isoxazolin-5-ones, N—H keto structures usually predominate,^{58, 324} and it would be surprising if they did not

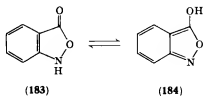
³²¹ D. L. Hammick, W. A. M. Edwardes, and E. R. Steiner, *J. Chem. Soc.* p. 3308 (1931); G. Englert, *Z. Elektrochem.* **65**, 854 (1961); F. B. Mallory and C. S. Wood, *Proc. Natl. Acad. Sci. U.S.A.* **47**, 697 (1961); A. R. Katritzky, S. Øksne, and R. K. Harris, *Chem. Ind. (London)* p. 990 (1961); R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. G. Paterson, *J. Chem. Soc.* p. 197 (1963).

³²² F. B. Mallory, K. E. Schueller, and C. S. Wood, *J. Org. Chem.* **26**, 3312 (1961).

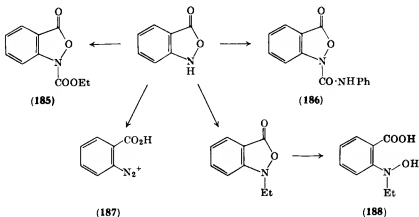
³²³ E. Bamberger and A. Fodor, *Ber. Deut. Chem. Ges.* **42**, 2573 (1909).

³²⁴ A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961); A. R. Katritzky, S. Øksne, and A. J. Boulton, *ibid.* **18**, 777 (1962).

also do so here. No examples of derivatives of the O—H form, e.g., 3-methoxyanthranil, are known.



2,1-Benzisoxazolin-3-ones are acidic, and are precipitated unchanged from solutions of their salts by mineral acids.¹⁴⁶ They may be alkylated,^{138, 146, 147} acylated,^{138, 145-147} and tosylated¹⁴⁶ on nitrogen. With formaldehyde they give the hydroxymethyl (126) and methylene-bis (127) derivatives. Ethyl chloroformate and phenyl isocyanate give **185** and **186**, respectively.¹⁴⁵ On heating, azobenzene-2,2'-dicarboxylic acid is formed.¹⁴⁶



Reductions with zinc and sulfuric acid or sodium hydroxide, sodium or aluminum amalgam, and ammonium sulfide, all lead to anthranilic acid.¹⁴⁶ Nitrous acid forms the diazonium salt (187), identified by its coupling reactions,¹³⁸ or in one case by reduction and recyclization to the corresponding indazolin-3-one.¹⁴⁷ Alkali hydrolyzes the *N*-ethyl derivative to the corresponding hydroxylamine (188), while oxidation (KMnO_4) gives *o*-nitrosobenzoic acid, with loss of the alkyl substituent.¹⁴⁶ The reaction of hydrazine with 2,1-benzisoxazolin-3-one

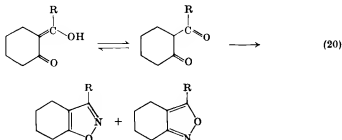
4-carboxylic acid proceeds with ring opening, recyclization, and reduction, to form 3-aminophthalic hydrazide (5-amino-1,2,3,4-tetrahydrophthalazine-1,4-dione).³²⁵

F. REDUCED DERIVATIVES

1. 4,5,6,7-Tetrahydroanthranils

These compounds form the largest group of reduced derivatives of anthranils. They are also referable to 3,4-disubstituted isoxazoles, and are prepared and react as such.

2-Acylcyclohexanones give a mixture of tetrahydro-1,2- and 2,1-benzisoxazoles with hydroxylamine.^{84,86,91,94,326} The former usually predominate, but when R = H [Eq. (20)] they may be removed by using their more ready decomposition with alkali.^{84,91}



β -Ketonitriles and hydroxylamine form 5-aminoisoxazoles; the appropriate 2-cyanocyclohexanones, therefore, form 3-amino-4,5,6,7-tetrahydroanthranils [Eq. (21)].^{100,327-329} The intermediate oximes may be isolated.³²⁷ 3-Aminotetrahydroanthranil may also be prepared from *o*-chlorocyclohexanone oxime and potassium cyanide.³³⁰ The

³²⁵ K. Gleu and K. Pfannstiel, *J. Prakt. Chem.* [2] **146**, 137 (1936).

³²⁶ G. Bianchi and P. Grunanger, *Chim. Ind. (Milan)* **46**, 425 (1964); *Chem. Abstr.* **60**, 15851 (1964).

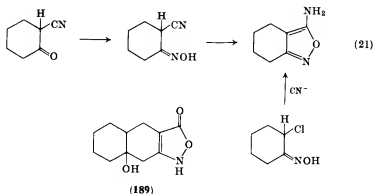
³²⁷ K. von Auwers, T. Bahr, and E. Frese, *Ann. Chem.* **441**, 68 (1925).

³²⁸ I. Satoda, T. Fukui, and K. Mori, *Yakugaku Zasshi* **79**, 961 (1959); *Chem. Abstr.* **53**, 21885 (1959). S. Suzuki, K. Ueno, and K. Mori, *Yakugaku Kenkyu* **34**, 224 (1962); *Chem. Abstr.* **57**, 16754 (1962).

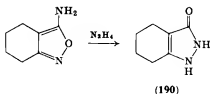
³²⁹ H. Morishita, S. Nakano, I. Satoda, N. Yoshida, and K. Mori (Nippon Shinyaku Co., Ltd.), Japanese Patent 5672 (1959); *Chem. Abstr.* **54**, 1546 (1960).

³³⁰ M. Ohno and N. Naruse, *Tetrahedron Letters* p. 2151 (1964).

tetrahydro-2,1-benzoxazolin-3-one (**189**) is formed from the corresponding β -keto ester.³³¹



The 3-amino derivatives have been converted into alkyl, acyl, and benzylidene derivatives.^{327,332} Sulfonamides have been prepared,^{100,328,329} and further reactions (alkylation and acylation³²⁸ and condensation with α -naphthoquinones³³³) performed upon these. The 3-amino compound is converted by hydrazine into tetrahydroindazolinone (**190**).³³⁴



3-Unsubstituted 4,5,6,7-tetrahydroanthranils are cleaved by alkali, although not so readily as the corresponding tetrahydroindoxazenes,

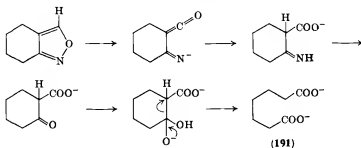
³³¹ W. Koch and F. Borkowsky, *Ber. Deut. Chem. Ges.* **70B**, 355 (1937).

³³² H. Kano and Y. Makizumi, *Yakugaku Zasshi* **76**, 1311 (1956); *Chem. Abstr.* **51**, 4357 (1957); H. Kano and N. Makizumi (Shionogi & Co.), Japanese Patent 9228 (1957); *Chem. Abstr.* **52**, 15592 (1958).

³³³ N. Steiger (Hoffmann-La Roche Inc.), U.S. Patent 2,555,614; *Chem. Abstr.* **45**, 10259 (1951).

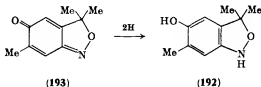
³³⁴ H. Kano, *Yakugaku Zasshi* **73**, 383 (1953); *Chem. Abstr.* **48**, 3342 (1954).

to pimelate salts (**191**).⁹¹ A possible route, similar to the anthranil decomposition in the first stages, is as follows:

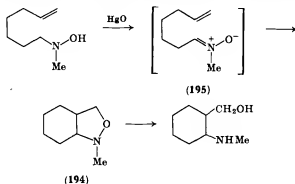


2. Other Reduced Derivatives

1,3-Dihydroanthranils have been reported, **86** as a reduction product of *o*-nitrobenzophenone,¹⁵¹ and **192** from the quinonoid compound (**193**).³³⁵ 3-Methylantranil dichloride has been shown to be a 4,5-dihydroanthranil (**139**).¹³⁵ A benzo derivative of this system is also known.⁸⁴



A series of octahydro derivatives, e.g., **194**, was obtained by intramolecular 1,3-dipolar cyclization of nitrones of type **195**. The com-



³³⁵ G. L. Buchanan, R. A. Raphael, and I. W. J. Still, *J. Chem. Soc.* p. 4372 (1963).

pounds were characterized as picrates, hydrogen oxalates, and methiodides, and their stereochemistry was investigated. Reduction (LiAlH_4 , Zn/HOAc , or H_2/Pt , Pd , or Ni) cleaved the N—O linkage.³³⁶

G. APPLICATIONS

5-Chloro-3-arylanthranils have found a use as intermediates in the preparation of substituted 2-aminobenzophenones.²²⁶ Some substituted 4,5,6,7-tetrahydro compounds have been stated to be useful in antihistamine synthesis,³³² and others tested against virus infections.³³³

IV. Note Added in Proof

The method of Lindemann and Thiele³⁴ for the synthesis of the parent indoxazene is a somewhat unsatisfactory one,^{337,338} and an alternative route devised by Kemp and Woodward,³³⁷ in which salicylaldehyde is treated with hydroxylamine-*O*-sulfonic acid, gives greatly improved yields. Quaternization of indoxazene has been achieved using triethyloxonium fluoroborate,³³⁷ and methyl 2,4-dinitrobenzenesulfonate.³³⁸ The *N*-ethyl salt reacts with nucleophiles X^- ($\text{X} = \text{SH}$, F , CN , OMe), the presumed intermediate (196) forming salicylic acid derivatives (197). With azide ion ($\text{X} = \text{N}_3$) the tetrazole (198) is formed, while the product with a carboxylate anion is the *O*-acyl derivative (199). Reaction with cyanate, thiocyanate, or thiourea gives benzoxazinedione derivatives (200) or (201).³³⁷ *N*-Methylindoxazanium 2,4-dinitrobenzenesulfonate is very readily hydrolyzed to *N*-methylsalicylamide;³³⁸ the *N*-ethylindoxazanium fluoroborate forms *N*-ethylsalicylamide similarly.³³⁷

Indoxazene-3-acetic acid has been prepared: its effectiveness in stimulating plant growth is only one hundredth that of indole-3-acetic acid.³³⁹

The reaction of enamines with nitrile oxides, forming hexahydro-(76) and tetrahydro-(77) indoxazenes,¹⁰⁵ has been used to prepare indoxazenes and naphthoisoxazoles, by dehydrogenating the reduced derivatives using *N*-bromsuccinimide.³⁴⁰ Addition of cyanogen di-*N*-oxide to cyclohexa-1,4-diene gives di-3a,4,7,7a-tetrahydro-

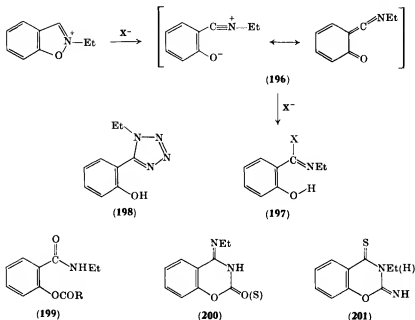
³³⁶ N. A. LeBel and J. J. Whang, *J. Am. Chem. Soc.* **81**, 6334 (1959); N. A. LeBel, M. E. Post, and J. J. Whang, *ibid.* **86**, 3759 (1964).

³³⁷ D. S. Kemp and R. B. Woodward, *Tetrahedron* **21**, 3019 (1965).

³³⁸ B. D. Wilson and D. M. Burness, *J. Org. Chem.* **31**, 1565 (1966).

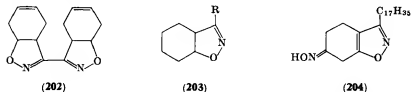
³³⁹ G. Cassini, F. Gualteri, and M. L. Stein, *J. Heterocycl. Chem.* **2**, 385 (1965).

³⁴⁰ P. Bianchi and E. Frati, *Gazz. Chim. Ital.* **96**, 559 (1966).



indoxazen-3-yl (202).³⁴¹ Nitrile oxides, prepared *in situ* without solvent, in the presence of an excess of cyclohexene, form 3a,4,5,6,7,7a-hexahydroindoxazenes (203).³⁴² The 4,5,6,7-tetrahydroindoxazene (204) has been obtained (along with an anthranil derivative: see below) from 3-ethoxy-6-stearoylcyclohex-2-en-1-one and hydroxylamine, and may be used as an antituberculous drug.³⁴³

An *N*-ethylindoxazinium salt (anion unspecified) has been used for the cyclization of oligopeptides.³⁴⁴ The procedure involves reaction



³⁴¹ C. Grundmann, V. Mini, J. M. Dean, and H. D. Frommheld, *Ann. Chem.* **687**, 191 (1965).

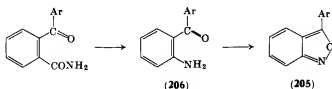
³⁴² G. Zinner and H. Günther, *Chem. Ber.* **98**, 1353 (1965).

³⁴³ N. Sugimoto, H. Kugita, M. Tanaka, and H. Inoue (Tanabe Seiyaku Co. Ltd.), Japanese Patent 20,704 (1965); *Chem. Abstr.* **64**, 2091 (1966).

³⁴⁴ S. Rajappa and A. S. Akerhar, *Tetrahedron Letters*, p. 2893 (1966).

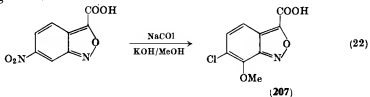
with the carboxyl group of the C-terminal amino acid of the N-protected peptide, reductive removal of the protecting group, and intermolecular cleavage of the *O*-acyl bond, giving cyclohexapeptides from tripeptides.

3-Arylanthranils (**205**) have been obtained from 2-arylbenezamides by Hofmann degradation and subsequent oxidation, using two moles of sodium hypobromite; besides (**205**), some brominated product was isolated. The anthranil (**205**) could be reduced (Zn/CaCl_2) to the amino ketone (**206**), which with nitrous acid gave some **205**, as well as the diazonium salt.³⁴⁵



The basicities of anthranil and its 3-methyl and 3,4-dimethyl derivatives have been determined: the $\text{p}K_a$ values are -2.22 , -1.24 , and -1.22 respectively. Ultraviolet data of these substances and their cations are recorded in the same paper.³⁴⁶

The "haloalkoxy substitution reaction" has been applied to 6-nitroanthroxanic acid [Eq. (22)], but 6-nitroanthranil decomposes to the anthranilic acid under the basic conditions of the reaction.³⁴⁷ Reduction of **207** with ferrous sulfate and ammonia yields the corresponding isatin.



3-Arylanthranils have been reduced with a new palladium catalyst to *o*-aminobenzophenones;³⁴⁸ lithium aluminum hydride gives the corresponding *o*-aminobenzhydrols in good yield.³⁴⁹

³⁴⁵ N. Campbell and H. F. Andrew, *Proc. Roy. Soc. Edinburgh*, Sect. A **66**, 252 (1963-4); *Chem. Abstr.* **62**, 16157 (1965).

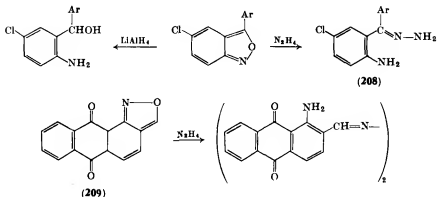
³⁴⁶ W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.*, p. 5360 (1965).

³⁴⁷ D. R. Eckroth, T. C. Cochran, and E. C. Taylor, *J. Org. Chem.* **31**, 1303 (1966).

³⁴⁸ F. Hoffman-La Roche & Co., A.-G., *Neth. Appl.* 6,407,011; *Chem. Abstr.* **63**, 583 (1965).

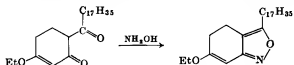
³⁴⁹ A. Hetzheim, H. Haack, and H. Beyer, *Z. Chem.* **6**, 218 (1966).

Hydrazine cleaves 3-phenyl-5-chloroanthranil to the hydrazone (208).³⁴⁹ An analogous reaction has been reported for the condensed anthranil (209).³⁵⁰



4,5,6,7-Tetrahydroanthranil has been obtained by the action of hydroxylamine on 2-dimethylaminomethylenecyclohexanone.³⁵¹

One of the reaction products of (210) and hydroxylamine is the 4,5-dihydroanthranil (211), which shows antituberculous activity.³⁴³



³⁵⁰ K. Wilke (Leopold Casella & Co., G.m.b.H.), German Patent 357,042 (1919).

³⁵¹ H. Bredereck, F. Effenberger, H. Botsch, and H. Rohn, *Chem. Ber.* **98**, 1081 (1965).

ACKNOWLEDGMENT

We thank Dr. J. L. Pinkus (University of Pittsburgh) for communicating to us some of his results in advance of publication.

TABLE I
INDOXAZENES



3	4	5	6	7	M.P. or B.P. (°C)	Ref.
—	—	—	—	—	86–87/11 mm; ⁴⁹ 82–83/14 mm; ³⁴ 90–92/15 mm ⁴⁹	34, 49
—	—	—	—	OMe	155–160/2 mm	67
—	—	—	OH	—	157	39
—	—	—	OAc	—	59	39
—	—	Cl	—	—	70	51
—	—	Cl	—	Cl	107	51
—	—	Br	—	Br	141 (dec.)	52
—	—	NO ₂	—	—	126; ³⁴ 126–127 ⁵¹	34, 51
—	—	NO ₂ ^a	OH	—	188	39
—	—	NO ₂ ^a	OAc	—	157	39
—	—	NO ₂ ^a	OH	NO ₂ ^a	114	39
—	—	NH ₂	—	—	74–75	39
—	—	NHAc	—	—	136	39
—	—	N=N—C ₁₀ H ₆ OH ^b	—	—	182	39
—	—	N=N—C ₁₀ H ₆ NH ₂ ^c	—	—	112	39
—	—	OPS(OEt) ₂	—	—	<i>d</i>	82
—	Me	—	Me	—	117/14 mm	38
—	Me	NO ₂ ^a	Me	—	112 ^e	38
—	Me	Br	Me	Br	185 (dec.)	52
—	Ac ^a	—	—	OMe	<i>f</i>	67

TABLE I—continued



3	4	5	6	7	M.P. or B.P. (°C)	Ref.
2,4-Dinitrophenylhydrazone					233	67
Me	—	—	—	—	95/12 mm; ⁴⁰	12, 19,
					104–108/15 mm; ¹²	40
					108–110/16 mm ¹⁹	
Me	—	—	—	OMe	185–190/2 mm	67
Me	—	—	—	NO ₂ ^a	250	34
Me	—	—	Me	—	122–124/14 mm	13
Me	—	—	Me	NO ₂ ^a	106–110	13
Me	—	—	Br	—	73–74	32
Me	—	—	I	—	114	32
Me	—	—	NO ₂	—	114	28, 31
Me	—	—	SO ₂ NMe ₂	—	141–142	32
Me	—	—	SO ₂ NEt ₂	—	98	32
Me	—	—	SO ₂ Pip ^c	—	144.5–145.5	32
Me	—	—	SO ₂ Morph ^b	—	178–180	32
Me	—	—	SO ₂ Ph	—	140–145	32
Me	—	Me	—	—	116/13 mm	12, 34
Me	—	Me	—	NO ₂ ^a	72	34, 40
Me	—	Me	—	NH ₂ ^a	110	40
Me	—	Me	—	OH ^a	247 (dec.)	40
Me	—	NO ₂	—	—	128; ³⁴ 129; ⁷ 134; ⁴⁰	7, 34, 40
					168–169/13 mm ⁴⁰	

Me	—	NO ₂	Me	—	161	13
Me	—	NH ₂	—	—	105	34
Me	—	NHAc	—	—	156; ³⁴ 163; ⁴⁰	34, 40
					215/12 mm ⁴⁰	
Me	—	N=N—C ₁₀ H ₆ OH ^b	—	—	<i>d</i>	34
Me	—	N=N—C ₁₀ H ₆ NH ₂ ^c	—	—	186	39
Me	—	OH	—	—	146	39
Me	—	OAc	—	—	76	39
Me	—	OMe	—	—	47; 147–8/13 mm	39
Me	Ac ^a	—	—	—	<i>f</i>	67
2,4-Dinitrophenylhydrazone	—	—	—	—	254	67
Me	Ac ^a	—	—	OMe	<i>f</i>	67
2,4-Dinitrophenylhydrazone	—	—	—	—	146	67
Me	Cl ^a	Me	—	NH ₂ ^a	147	39
Et	—	—	—	—	<i>i</i>	12
CH ₂ Ph	—	—	—	—	87	12
CH ₂ COOH	—	—	—	—	106–108 (dec.)	339
CH ₂ COOH	—	—	Me	—	167–171	35 ⁱ
CH ₂ COOH	—	Me	—	—	155 (dec.)	35 ^j
Ac	—	—	NO ₂	—	135–136	27
Phenylhydrazone	—	—	—	—	192–193	27
COPh	—	—	NO ₂	—	157–158	27
Ph	—	—	—	—	80; ¹⁶ 181/13 mm; ²⁰	5, 9, 15,
					81–82; ⁶⁴ 83; ^{9, 55}	16, 20,
					83–84 ^{5, 36, 37, 56, 66}	36, 37, 55,
					331–336/15 mm; ¹⁵	56, 64, 66
x,x-Dibromo compound	—	—	—	—	148–149	69
x,x-Dinitro compound	—	—	—	—	239–241	15
x,x-Disulfonic acid	—	—	—	—	<i>d</i>	69
x,x-Disulfonamide	—	—	—	—	187–188	69
Ph	—	—	—	Me	147–150/1 mm	41
x,x-Dinitro compound	—	—	—	—	225.5–226.5	41
Ph	—	—	—	OMe	58; 230–240/2 mm	67
Ph	—	—	NO ₂	—	139	18

TABLE I—continued



3	4	5	6	7	M.P. or B.P. (°C)	Ref.
Ph	—	Me	—	—	92–93	42
Ph	—	NO ₂	—	—	143	7
Ph	—	Br ^a	—	—	88–89	9
Ph	—	NO ₂	—	NO ₂	242–243 (dec.)	7
Ph	Ac ^a	—	—	OMe	187	67
2,4-Dinitrophenylhydrazone	—	—	—	—	278	67
Ph	COPh ^a	—	—	OMe	195	67
Ph	Br ^a	—	—	OMe	150	67
Ph	NO ₂ ^a	—	—	OMe	194	67
C ₆ H ₄ —Me ^k	—	—	—	—	81–82	6
C ₆ H ₄ —Br(<i>p</i>)	—	—	—	—	132–133	6
C ₆ H ₄ —OMe ^k	—	—	—	—	100–101	6
C ₆ H ₄ —OEt ^k	—	—	—	—	59–60	6
C ₆ H ₄ —NO ₂ (<i>m</i>)	—	—	—	—	171–172	340
C ₆ H ₄ —NO ₂ (<i>p</i>) ^a	—	NO ₂ ^a	—	—	238–239	9
C ₆ H ₄ —Ph(<i>p</i>)	—	—	—	—	119–120	9
C ₆ H ₄ —Ph(<i>o</i>)	—	—	—	—	100–101	9 ^l
C ₆ H ₃ Cl ₂ (2,4)	—	—	—	—	78	8
C ₆ H ₃ —OMe(2)—Me(5)	—	—	^l —	—	170/0.5 mm	8
C ₆ H ₃ —OH(2)—Me(5)	—	NO ₂	—	—	148	8 ^l
—(<i>p</i>)C ₆ H ₄ —C ₆ H ₄ (<i>p</i>)—	—	—	—	—	235–236	9
C ₁₀ H ₇ ^{k, l}	—	—	—	—	92–93	11

^a Position uncertain.^b 2'-Hydroxy-1'-naphthyl.^c 2'-Amino-1'-naphthyl.^d No data.^e Rapid heating.^f Oil; no further data.^g 1-Piperidino-.^h 4-Morpholino-.ⁱ Isolated as crude material only.^j Indoxazene structure questionable.^k Position of substitution not indicated.^l Naphthyl-.

TABLE II
INDOXAZENE-3-CARBOXYLIC ACIDS AND DERIVATIVES



X	4	5	6	7	M.P. (°C)	Ref.
OH	—	—	—	—	140–141	46
OH	—	—	NH ₂	—	160 (dec.)	46
OH	—	—	NHAc	—	<i>a</i>	46
OH	—	—	Cl	—	171 (dec.)	46
OMe	—	—	—	—	69	46
OMe	—	—	NH ₂	—	202 ⁶⁸ ; 206 ⁴⁶	46, 68
OMe	—	—	NHAc	—	208 ⁶⁸ ; 210 ⁴⁶	46, 68
OMe	—	—	NAc ₂	—	130	46
OMe	—	—	NHCOPh	—	206	68
OMe	—	—	NH—SO ₂ Ph	—	188	68
OMe	—	—	NH—Ts	—	203	68
OMe	—	—	NH—Sulf-Ac	—	233	68
OMe	—	—	N=N—C ₆ H ₄ —NMe ₂ (<i>p</i>)	—	210	68
OMe	—	—	Cl	—	124	46
OMe	—	—	C ₁₀ H ₁₂ NO ₂ ^c	—	262 (dec.)	68
OMe	—	—	C ₁₈ H ₁₄ NO ₃ ^d	—	200	68
OMe	—	NO ₂ ^c	NHAc	—	189	68

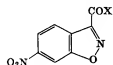
TABLE II—continued



X	4	5	6	7	M.P. (°C)	Ref.
OMe	—	Br ^c	NHAc	—	215	68
OMe	—	Br ^c	NHCOPh	—	185	68
OEt	—	—	—	—	101–102	26
OEt	—	—	NH ₂	—	147	46
OEt	—	—	NHAc	—	186–187	46
OPr	—	—	NHAc	—	<i>f</i>	108
NH—NH ₂	—	—	—	—	143	46
NH—NH ₂	—	—	Cl	—	192 (dec.)	46
NH—NH ₂	—	—	NHAc	—	218	46
N ₃	—	—	—	—	95 (dec.)	46
N ₃	—	—	Cl	—	142 (dec.)	46
N ₃	—	—	NHAc	—	155 (dec.)	46

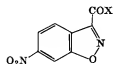
^a Rearranges on heating.^b SO₂—C₆H₄—NHAc(*p*).^c 2,3-Diketo-4,5-diphenylpyrrolidino-(1)-.^d 2-Keto-3-acetoxy-4,5-diphenyl-Δ³pyrrolino-(1)-.^e Position uncertain.^f No data.

TABLE III
DERIVATIVES OF 6-NITROINDOXAZENE-3-CARBOXYLIC ACID



X	Derivative	M.P. (°C)	Ref.
OH	—	189–190	70
OMe	—	120; ⁷³ 126; ³³ 129–130; ²⁹ 130–131 ^{26, 27, 30}	26, 27, 29, 30, 33, 73
OEt	—	99–100	71, 77
OPr	—	<i>a</i>	77
OBu	—	<i>a</i>	77
O— <i>i</i> -Bu	—	<i>a</i>	77
O— <i>n</i> -Hex	—	60–62	71
O—(CH ₂) ₂ —NMe ₂	Hydrochloride	172–173 (dec.)	71, 77
	Picrate	194–195	71
O—(CH ₂) ₂ —NEt ₂	Hydrochloride	152–153 (dec.)	71, 77
	Picrate	160.5–161.5 (dec.)	71
O—(CH ₂) ₂ —NBu ₂	—	<i>a</i>	77
O—(CH ₂) ₂ —Pip ^b	Hydrochloride	160–161 (dec.)	71, 77
	Picrate	208–210 (dec.)	71
O—(CH ₂) ₂ —(2-Me—Pip ^b)	Hydrochloride	151–151.5 (dec.)	71, 77
	Picrate	196–197.5	71
O—(CH ₂) ₂ —(2,6-Me ₂ —Pip ^b)	—	<i>a</i>	72

TABLE III—continued



X	Derivative	M.P. (°C)	Ref.
O—(CH ₂) ₂ —(3-Et—Pip ^b)	—	<i>a</i>	77
O—(CH ₂) ₂ —Morph ^c	—	<i>a</i>	72
O—(CH ₂) ₂ —(2,5-Me ₂ —Pyrr ^d)	—	<i>a</i>	77
O—CHMe—CH ₂ —NMe ₂	—	<i>a</i>	77
O—(CH ₂) ₃ —NEt ₂	Hydrochloride	151.5–152	71, 77
	Picrate	202–202.5	71
O—(CH ₂) ₃ —Pip ^b	Hydrochloride	189–190.5	71, 77
	Picrate	210–211.5	71
O—(CH ₂) ₃ —(4-Me—Pip ^b)	—	<i>a</i>	77
O—(CH ₂) ₃ —(2-Me—Pip ^b)	Hydrochloride	158–158.5	71, 77
	Picrate	177–180.5	71
O—(CH ₂) ₃ —(2,6-Me ₂ —Pip ^b)	—	<i>a</i>	77
O—(CH ₂) ₃ —Morph ^c	—	<i>a</i>	77
O—(CH ₂) ₃ —Pyrr ^d	—	<i>a</i>	77
O—(CH ₂) ₃ —(2-Me—Pyrr ^d)	—	<i>a</i>	77
O—(CH ₂) ₃ —(2,5-Me ₂ —Pyrr ^d)	—	<i>a</i>	77
O—(CH ₂) ₄ —NMe ₂	—	<i>a</i>	77
O—(CH ₂) ₄ —NEt ₂	—	<i>a</i>	77
NH—NH ₂	—	170; ⁷⁰ 174–177 ⁶³	63, 70

N ₃	—	90 (dec.); ⁶³ 135 (dec.) ⁷⁰	63, 70
NH ₂	—	189–190	27
Pip ^b	—	110–111	71
NH—(CH ₂) ₂ —NEt ₂	—	61–63	77
	Hydrochloride	227–228.5	77
	Picrate	174–175	71, 77
NH—(CH ₂) ₂ —NBu ₂	—	<i>a</i>	77
NH—(CH ₂) ₂ —(3-Et—Pip ^b)	—	<i>a</i>	77
NH—(CH ₂) ₂ —(2,5-Me ₂ —Pyrr ^d)	—	<i>a</i>	77
NH—(CH ₂) ₂ —OH	—	153–153.5	71
NH—CHMe—CH ₂ —NMe ₂	—	<i>a</i>	77
NH—(CH ₂) ₃ —NEt ₂	—	89–89.5	77
	Hydrochloride	232.5–233.5 (dec.)	77
	Picrate	161.5–163.5	71
	Methiodide	204–206	77
NH—(CH ₂) ₃ —(4-Me—Pip ^b)	—	<i>a</i>	77
NH—(CH ₂) ₃ —(2,6-Me ₂ —Pip ^b)	—	<i>a</i>	77
NH—(CH ₂) ₃ —Morph ^c	—	<i>a</i>	77
NH—(CH ₂) ₃ —Pyrr ^d	—	<i>a</i>	77
NH—CH ₂ —CHOH—CH ₂ NEt ₂	—	120–120.5	77
	Hydrochloride	209–209.5	77
	Picrate	206–206.5	71
	Methiodide	174.5–176	77
NH—(CH ₂) ₄ —NMe ₂	—	<i>a</i>	71, 77
NH—(CH ₂) ₄ —NEt ₂	—	59–60	77
	Hydrochloride	173–175	77
	Picrate	127.5–128	77

^a No data.^b 1-Piperidino-.^c 4-Morpholino-.^d 1-Pyrrolidino-.

TABLE IV
3-AMINOINDOXAZENE AND DERIVATIVES



R ₁	R ₂	4	5	6	7	M.P. or <u>B.P.</u> (°C)	Ref.
—	—	—	—	—	—	110; 46, 78 111 ^{44, 45}	44, 45
—	—	—	—	—	OMe	142.5; 126/0.01 mm	46, 78
—	—	—	—	—	CH ₂ —CH=CH ₂	100	44
—	—	—	—	Cl	—	135; 45, 47 122–125/0.01 mm ⁴⁵	44, 46
—	—	—	—	NO ₂	—	234	63, 70
—	—	—	—	NH ₂	—	141	46, 70
—	—	—	—	NHAc	—	222	46
—	—	—	Cl	—	—	142; 125/0.1 mm	44
—	—	—	Cl	—	Cl	161; 154/0.1 mm	44

—	—	—	Br	—	Br	185	44
—	—	—	NO ₂	—	—	208	44
—	—	—	NO ₂	—	NO ₂	226	44
—	—	—	CMe ₂ —CH ₂ —CMe ₃	—	—	149.5	44
Ac	—	—	—	—	—	155–156; ⁴⁶ 160 ⁴⁴	44, 46
Ac	—	—	—	Cl	—	186	46
Ac	—	—	—	NO ₂	—	230 ^a	70
Ac	—	—	—	NHAc	—	256	46
Ac	Ac	—	—	NO ₂	—	133	70
—CO— ^b	—	—	—	—	—	244	46
—CO— ^b	—	—	—	Cl	—	260	46
—CO— ^b	—	—	—	NO ₂	—	342	70
COOPr	—	—	—	NH ₂	—	138 (dec.)	46
COOPr	—	—	—	NHAc	—	205 (dec.)	46
COOBu	—	—	—	NH ₂	—	104 (dec.)	46
COOBu	—	—	—	NHAc	—	248	46
COO- <i>i</i> -Am	—	—	—	NH ₂	—	145	46
COO- <i>i</i> -Am	—	—	—	NHAc	—	215	46
COOCH ₂ Ph	—	—	—	NO ₂	—	191–192.5	63

^a Not sharp.^b Bis-3-indoxazenylylurea.

TABLE V
3-HYDROXYINDOXAZENE AND DERIVATIVES



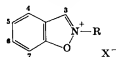
X	4	5	6	7	M.P. (°C)	Ref.
—	—	—	—	—	143	48
—	—	—	—	Me	161.5	48
—	—	—	—	OMe	203	48
—	—	—	Me	—	154.5	48
—	—	—	OMe	—	209	48
—	—	—	Cl	—	217.5	48
—	—	—	NO ₂	—	223.5	48
—	—	—	NO ₂	—	85–88 ^a	70 ^b
—	—	—	NHAc	—	160–165 ^a	46
—	—	Cl	—	—	215	48
—	—	Cl	—	Cl	227	48
—	—	Br	—	Br	245.5	48
—	—	Br	—	Br	154–158	54 ^a
—	—	I	—	I	265	48
—	—	NO ₂	—	—	202	48
—	—	<i>t</i> -Bu	—	—	166.5	48
—	—	SMe	—	—	147	48
PO(OEt) ₂	—	—	—	—	<i>c</i>	81
PS(OEt) ₂	—	—	—	—	<i>c</i>	81
PS(OMe) ₂	—	—	—	—	<i>c</i>	81
PS(Et)(OEt)	—	—	—	—	<i>c</i>	81
PS(OEt) ₂	—	Cl	—	—	<i>c</i>	81

^a Crude product.

^b Structure questionable.

^c No data.

TABLE VI
QUATERNARY INDOXAZENIUM SALTS



R	3	4	5	6	7	X	M.P. (°C)	Ref.
Me	—	—	—	—	—	C ₆ H ₅ N ₂ O ₇ S ^a	141–143	338
Me	Ph	—	—	—	—	FeCl ₄	117–119	65
Me	NH ₂	—	—	NO ₂	—	I	211–212 (dec.)	63
Me	NH ₂	—	—	NH ₂	—	I	244 (dec.)	63
Me	NH ₂	—	—	NH—Pyrim ^b	—	I	235–245 (dec.)	63
Me	NH ₂	—	—	NH—Pyrim ^b	—	Cl	260 (dec.)	63
Me	Ph	—	Me	—	—	FeCl ₄	95–96	62
Et	—	—	—	—	—	BF ₄	109.5–110	337
Et	Me	—	—	—	—	I	157–158	83
Et	Ph	—	—	—	—	Cl	95–97	64
Et	Ph	—	—	—	—	ClO ₄	183–184	64
Et	Ph	—	—	—	—	FeCl ₄	134	64
Et	Ph	—	—	—	—	HgCl ₃	119–120	64
Et	Ph	—	—	—	—	C ₆ H ₅ N ₃ O ₇ ^c	132–133	64
Et	CH=CH—NHPh	—	—	—	—	I	215–217	83
Et	(CH=CH) ₂ —NAc—Ph	—	—	—	—	I	213	83
CH ₂ Ph	Ph	—	—	—	—	ClO ₄	164–165	65
(CH ₂) ₂ —COOH	Me	—	—	—	—	I	174–176	83
(CH ₂) ₃ —SO ₃ ⁻	CH=CH—NHPh	—	—	—	—	—	<i>d</i>	83

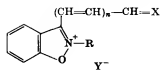
^a 2,4-Dinitrobenzene sulfonate.

^b 2-Amino-3,4-dimethylpyrimidyl-(6)-.

^c Picrate.

^d No data.

TABLE VII
INDOXAZENE CYANINES



R	Y	n	X	M.P. (°C)	λ_{\max} (MeOH) (m μ)	Sens. Max. (m μ)	Ref.
Et	I	1		215	504	530	83
Et	I	1		258-261	496	530	83
Et	I	2		201-203	545	585	83
Et	I	1		255-256	507	545	83
Et	I	2		197-198	600	640	83


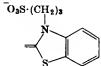

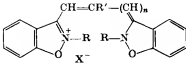
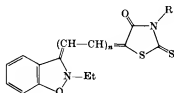
$(\text{CH}_2)_3\text{—SO}_3^-$	—	1		302–303	515	540	83
Et	—	1		311–313	—	550	83
Et	I	1		{ 266–267 312–313	594 593	620 670	83 83
$(\text{CH}_2)_3\text{—SO}_3^-$	—	1					
							
R	R'	n	X	M.P. (°C)	λ_{max} (MeOH) (m μ)	Sens. Max. (m μ)	Ref.
Et	H	1	I	261	483	510	83
Et	Me	1	I	269–270	487	514	83
Et	Et	1	I	267–269	484	520	83
Et	H	3	I	164–165	578	620	83
$(\text{CH}_2)_2\text{—COOH}$	H	3	I	181	578	615	83

TABLE VIII
INDOXAZENE MEROCYANINES



R	n	M.P. (°C)	λ_{max} (MeOH) (m μ)	Sens. Max. (m μ)	Ref.
Et	1	235	493	550	83
CH ₂ COOH	1	280-281	489	552	83
Et	2	264-265	577	650	83

TABLE IX
 CONDENSED INDOXAZENE SYSTEMS

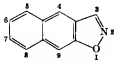
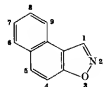
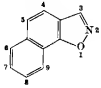
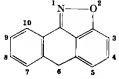
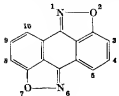
Ring system	Substituents	M.P. (°C)	Ref.
Naphth[2,3- <i>d</i>]isoxazole	3-NH ₂ 3-OH	210 234	45 48
			
Naphth[1,2- <i>d</i>]isoxazole	— x-NO ₂ 3-Ph	83 165-167 62-63	39 39 340
			
Naphth[2,1- <i>d</i>]isoxazole	3-Ph	87.5; ⁴⁵ 133 ³⁴⁰	45 340
			
6 <i>H</i> -Anthra[9,1- <i>cd</i>]isoxazole	6=O 6=O, 7-Cl	298.5 229	14 14
			
Anthra[9,1- <i>cd</i> ;10,5- <i>c'd'</i>]diisoxazole	—	304	14
			

TABLE X
4,5,6,7-Tetrahydroindoxazenes



3	4	5	6	7	M.P. or B.P. (°C)	Ref.
—	—	—	—	—	90–92/13 mm ^a	90, 91
HgCl ₂ adduct	—	—	—	—	135	91
—	—	—	—	Me	85–86/11 mm; ⁹¹ 101 ⁵⁶	56, 91
HgCl ₂ adduct	—	—	—	—	66	91
—	—	—	C ₆ H ₄ —OMe(<i>p</i>)	CH ₂ COOMe	145–150/6 × 10 ⁻³ mm	87, 89
—	—	—	C ₆ H ₄ —OMe(<i>p</i>)	Me	<i>b</i>	86
—	—	CH(OMe) ₂	—	—	<i>b</i>	90
—	—	OCH ₂ Ph	—	—	<i>b</i>	85
—	Me	—	—	<i>i</i> -Pr	<i>b</i>	84
Me	≡O	—	—	—	66–67	92
C ₁₇ H ₃₅	—	—	≡NOH	—	113–115	343
Ph	—	—	—	—	50; ¹⁰⁵ 53–54; ¹⁰⁵ 64 ⁹³	93, 105
Ph	—	CH ₃	—	—	60	340
C ₆ H ₄ —NO ₂ (<i>m</i>)	—	—	—	—	126	340
C ₆ H ₄ —NO ₂ (<i>p</i>)	—	—	—	—	180	105
COOH	—	—	—	—	128; ¹⁰⁵ 130 ⁹⁴	94, 105
COCl	—	—	—	—	<i>b</i>	94
COOEt	—	—	—	—	112–114/3 mm	95
Hydrochloride	—	—	—	—	118–119	95

COOEt	—	Me	—	—	153–154/6 mm	95
CONH ₂	—	—	—	—	160	95
CONEt ₂	—	—	—	—	137/10 mm	94
CONH—NH ₂	—	—	—	—	105–106	98
CONH—NH ₂	—	Me	—	—	184–185	98
CONH—N=CH—Ph	—	—	—	—	222–223	96, 97, 98
CONH—N=CH—Ph	—	Me	—	—	181–182	98
CONH—N=CH—C ₆ H ₄ —OMe(<i>p</i>)	—	—	—	—	180–181	98
CONH—N=CH—C ₆ H ₄ —Cl(<i>p</i>)	—	—	—	—	191	98
CONH—N=CMe ₂	—	—	—	—	99–100	98
CONH—N=CMe—Ph	—	—	—	—	173–174	98
CONH—NH—CH ₂ Ph	—	—	—	—	86–88	96, 97
Hydrochloride	—	—	—	—	202	96
CONH—NH—CH ₂ Ph	—	Me	—	—	<i>c</i>	96, 97
Hydrochloride	—	—	—	—	186–187	96, 97
CONH—NH—CH ₂ —C ₆ H ₄ —OMe(<i>p</i>)	—	—	—	—	95–96	96, 97
CONH—NH—CH ₂ —C ₆ H ₄ —Cl(<i>p</i>)	—	—	—	—	127.5	97
CONH—N=CH—C ₆ H ₄ —NMe ₂ (<i>p</i>)	—	—	—	—	233 (dec.)	98
CONH—NH—CHMe ₂	—	—	—	—	85–86	96, 97
CONH—NH—CHMe—Ph	—	—	—	—	82–83	96, 97
CON(CH ₂ Ph)—NH ₂	—	—	—	—	118–119	98
CONH—N(CH ₂ Ph)—CO—Isox ^d	—	—	—	—	144–145	98
CONH—N(CH ₂ Ph)—CO—Indox ^e	—	—	—	—	129–130	98
NH ₂	—	—	—	—	139	98, 99
NH—SO ₂ —C ₆ H ₄ —NH ₂ (<i>p</i>)	—	—	—	—	<i>c</i>	100

^a Crude product.^b Not isolated pure.^c No data.^d 5-Methylisoxazol-3-yl^e 4,5,6,7,-Tetrahydroindoxazen-3-yl.

TABLE XI
OTHER REDUCED INDOXAZENES



Position of extra hydrogen	Substituents	M.P. or <u>B.P.</u> (°C)	Ref.
2,3	2-Ph, 7-Ph	103-103.5	106
2,3	2-Me, 3-Ph	59-59.5	107
4,5	6-C ₆ H ₄ -OMe(<i>p</i>), 7-CH ₂ COOMe	77-79; ⁸⁹ 145-150/5 × 10 ⁻³ mm ^{87, 89}	87, 89
4,5	6-C ₆ H ₄ -OMe(<i>p</i>), 7-CH ₂ COOH	184.5-185.5	101
4,5	6,7-Benzo ^a	163/11-12 mm	102
HgCl ₂ adduct		142	102
4,5	3-Ph, 6,7-Benzo	112	340
4,5	6,7-Naphtho-(1,2) ^b	110-110.5	84

4,5	6,7-Naphtho-(2,1) ^c	94-95	84
4,7	3-Ph, 4=O, 7=O	240-241	103
4,7	3-Ph, 4=O, 5,6-Benzo, 7=O	139	103
6,7	3-Ph, 4,5-Benzo	88	340
3a,4,5,7a	3-Ph, 6,7-Benzo, 7a-Pyrr ^d	148	340
3a,4,7,7a	3-Indox ^a	176 (dec.)	341
3a,6,7,7a	3-Ph, 4,5-Benzo, 7a-Pyrr ^d	241	340
3a,4,5,6,7,7a	3- <i>t</i> -Bu	50-52	342
3a,4,5,6,7,7a	3-Ph	78-80	342
3a,4,5,6,7,7a	3-Ph, 7a-Morph ^f	91-92	340
3a,4,5,6,7,7a	3-Ph, 5-Me, 7a-Pyrr ^d	88-89	340
3a,4,5,6,7,7a	3-C ₆ H ₄ -NO ₂ (<i>m</i>), 7a-Pyrr ^d	96-97	340
3a,4,5,6,7,7a	3-Ph, 4=NOH	167-168	104
3a,4,5,6,7,7a	3-Ph, 7a-Pyrr ^d	103-104	105
3a,4,5,6,7,7a	3-Ph, 7a-Pip ^e	132-133	105
3a,4,5,6,7,7a	3-Ph, 7a-Morph ^f	<i>g</i>	105
3a,4,5,6,7,7a	3-Ph, 7-Me, 7a-Pyrr ^d	163-164	105
3a,4,5,6,7,7a	3-C ₆ H ₄ -NO ₂ (<i>p</i>), 7a-Morph ^f	138-140	105

^a 4,5-Dihydronaphth[2,1-*d*]isoxazole.^b 10,11-Dihydrophenanthro[2,1-*d*]isoxazole.^c 4,5-Dihydrophenanthro[3,4-*d*]isoxazole.^d 1-Pyrrolidino-.^e 1-Piperidino-.^f 4-Morpholino-.^g Not isolated pure.^h 3a,4,7,7a-Tetrahydroindoxazen-3-yl.

TABLE XII

ANTHRANILS



	3	4	5	6	7	M.P. or <u>B.P.</u> (°C)	Ref.
—	—	—	—	—	—	99–99.5/13 mm; ¹⁶⁶ 210–215 (dec.) ¹⁰⁰	109, 166
HgCl ₂ adduct	—	—	—	—	—	174 (dec.); ¹⁰⁹ 178; ¹⁵⁵ 178–178.5; ^{137, 166, 186, 187} 180–185 ²⁶⁸	109, 137, 155, 166, 186, 187, 268
Picrate	—	—	—	—	—	233–237	268
—	—	—	—	—	NO ₂	144–145	135, 270
—	—	—	—	—	Cl	61.5–62	135
—	—	—	—	—	NO ₂	133	179, 180
HgCl ₂ adduct	—	—	—	—	—	158	181
Hydrazine adduct	—	—	—	—	—	175	179, 180
—	—	—	Me	—	Me	a	187
—	—	—	Cl	—	—	79–79.5	269, 270
—	—	—	Br	—	—	88.5	269, 270
—	—	—	NO ₂	—	—	120–121	135, 270
—	—	—	—CH ₂ —O—CH ₂ —	—	—	110.5	117
HgCl ₂ adduct	—	—	—	—	—	238	117
—	—	—	OMe	OAc	Anthr'	211	139
—	—	—	—	NO ₂	—	134	182
HgCl ₂ adduct	—	—	—	—	—	149	182
Hydrazine adduct	—	—	—	—	—	165	182

—	Cl	—	—	Cl	96-97; ¹¹⁷	112.5-113 ¹⁸⁷	117, 187
—	NO ₂	—	—	NO ₂	—	122-124	242
—	Br	—	—	NO ₂	—	125	182
HgCl ₂ adduct						156	182
Hydrazine adduct						163	182
—	I	—	—	NO ₂	—	123	182
HgCl ₂ adduct						163	182
Hydrazine adduct						178	182
—	—	—	—	OMe	<i>a</i>	—	117
HgCl ₂ adduct						185	117
—	COOH	OH	—	OMe	—	174-175	116
—	COOH	OMe	—	OMe	—	183-184; ¹¹⁸ 184; ¹¹³	113, 115, 118
						200 ¹¹⁵	
—	COOH	OAc	—	OMe	—	198	114 ^b
—	COOMe	OMe	—	OMe	—	127	115
—	COOEt	OMe	—	OMe	—	98	115
Me	—	—	—	—	—	91/1 mm ³⁴⁶ ;	56, 120, 122, 346
						110.5-111/10 mm; ¹²²	
						121/17 mm; ⁵⁶	
						121-122/17 mm ¹²⁰	
HgCl ₂ adduct						167; ¹²² 169.5 ^{122, 137, 164}	122, 137, 164
Me	—	—	—	NO ₂	—	165-166	238
Me	—	—	—	Cl	—	56-57	135
Me	—	—	—	Ac	—	113-114	123
Me	—	Cl	—	—	—	97; ¹³⁵ 97.5-98 ¹²²	122, 135
HgCl ₂ adduct						183.5	122
Me	—	Br	—	Br	Br	116	286
HgCl ₂ adduct						<i>d</i>	286
Me	—	Br	—	Br	Br	<i>e</i>	286
Me	—	OMe	—	OMe	—	130; ¹³⁰ 133 ¹²²	124, 132
Me	—	NO ₂	—	—	—	145-146	135, 270
Me	Me	—	—	—	—	82	346

TABLE XII—*continued*

3	4	5	6	7	M.P. or <u>B.P.</u> (°C)	Ref.
Me	COOH	—	—	—	195	125
Me	Me	Isox ^f	Me	—	109–110.5	239
CH ₂ COOH	—	—	—	—	106–107; ¹⁸⁵ 108 ¹⁸³	163, 165
CH=H ₂ d ^e	—	—	—	—	202–203	305
CH ₂ —CHNH ₂ —COOH ^a	—	—	—	—	213–215 (dec.)	305
CH ₂ —NMe—Ts	—	OMe	OMe	—	~ 184	132
CHO	—	—	—	—	72.5	183
CH=NOH	—	—	—	—	172–173	163
CH=N—Ph	—	—	—	—	~ 40	183
CO—CH ₂ Cl	—	—	—	—	103–104	164
CO—CHN ₂	—	—	—	—	115	164
COPh	—	—	—	—	94; ³⁰⁶ 95.5–96 ²³⁶	236, 306
COPh	—	—	NO ₂	—	151–152	306 ^f
COPh	—	—	COOEt	—	100.5	306 ^f
CO—C ₆ H ₂ Cl ₂ (3,5)—NO ₂ (2)	—	—	—	—	177	306 ^f
CO—Py ^e	—	—	—	—	105–107	307 ^f
C(=NOH)—Ph	—	—	—	—	<i>d</i>	235
C(OH)Ph ₂	—	—	—	—	122.5–124.5	235, 236

COOH	—	—	—	—	187-195; ²²⁷ 190-191 (dec.); ¹⁸⁷ 191-192; ²²³ 192; ²²¹ 196; ^{178, 230} 197 ¹⁴² ; 197-198 ^{164, 229} 197.5; ¹⁴² 200 ¹⁵⁶	142, 156, 164, 178, 187, 221, 223, 227, 229, 230
Strychnine salt					210-212	252
Quinine salt					189-202	252
Brucine salt					210-212	252
COOH	—	—	OMe	OMe	168-169 (dec.); ¹⁷⁸ 175 (dec.) ¹⁷⁷	177, 178
COOH	—	—	NO ₂	—	171-172 (dec.)	347
COOH	—	—	Cl	OMe	182 ^a	347
COOH	—	Br	—	—	202-203 (dec.)	159
COCl	—	—	—	—	44	164
COOMe	—	—	—	—	67-68; ²²⁷ 70 ^{143, 164}	143, 164, 227
COOEt	—	—	—	—	64-65; ¹⁴³ 66-67 ²²⁷	143, 227
CONH ₂	—	—	—	—	211-212; ¹⁶⁰ 213 ²²⁹	160, 229
CONH- <i>i</i> -Pr	—	—	OMe	OMe	92-93	178
CONH-(CH ₂) ₂ -Ph	—	—	OMe	OMe	123-124	178
CN	—	—	—	—	58-59	227
NH ₂	—	—	—	—	110-114	150
C ₄ H ₃ S ^k	—	—	—	—	77-78	129
HgCl ₂ adduct					<i>d</i>	129
Picrate					<i>d</i>	129
C ₄ H ₃ O ^l	—	—	—	—	101.5-102	130
Py ^j	—	—	—	—	124-125	131
C ₁₀ H ₇ ^m	—	—	—	—	330	195

^a Oil; no further data.

^b Structure doubtful.

^c 6-Acetoxy-5-methoxyanthranilyl-(7)-.

^d No data.

^e Not isolated pure.

^f 5-Methylisoxazolyl-(3)-.

^g Hydantoin.

^h Racemate.

ⁱ Structure based on analogy.²³⁶

^j Pyridyl-(4)-.

^k Thienyl-(2)-.

^l Furyl-(2)-.

^m Naphthyl-(2)-.

ⁿ Hydrochloride.

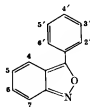
^o Pyridyl-(2)-.

Sec. V.]

INDOXAZINES AND ANTHRANILS

367

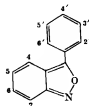
TABLE XIII
3-PHENYLANTHRANILS



Phenyl substituent	4	5	6	7	M.P. (°C)	Ref.
—	—	—	—	—	52–53; ^{37, 126} 53–53.5 ¹⁸⁸	37, 126, 188
HgCl ₂ adduct	—	—	—	—	195–198; ¹⁸⁸ 200 ³⁷	37, 188
Picrate	—	—	—	—	<i>a</i>	126
—	—	—	NO ₂	—	172; ²⁰¹ 174–175 ¹⁹⁰	196, 201
HgCl ₂ adduct	—	—	—	—	185–190 (dec.)	196
—	—	—	NH ₂	—	135–136	196
HgCl ₂ adduct	—	—	—	—	192	196
—	—	—	NHCOPh	—	260	196
—	—	Cl	—	—	114–116; ^{224, 225} 116–117 ¹⁶¹	161, 224, 225
—	—	Cl	Cl	—	157–158	224
—	—	Br	—	—	116–118	224
—	—	OMe	OMe	—	127.5–128.5	128
HgCl ₂ adduct	—	—	—	—	195–207	128
—	COOH	—	—	—	225	127
4'-Me	—	—	—	—	95.5	194
HgCl ₂ adduct	—	—	—	—	<i>a</i>	194
4'-Me	—	—	NO ₂	—	211	195

4'-F	—	—	NO ₂	—	a	198
4'-Cl	—	—	—	—	152; ²⁷⁹ 156-168 ²³⁷	237, ^b 279
4'-Cl	—	—	NO ₂	—	215	197
4'-Cl	—	Cl	—	—	202; ²¹⁶ 214-215 ²²⁴	216, 224
4'-Cl	—	Br	—	—	213-215	224
4'-Br	—	—	—	—	155	345
HgCl ₂ adduct	—	—	—	—	222-223	345
4'-Br	—	—	NO ₂	—	210-211	195
4'-Br	—	Br ^c	—	—	220-222	345
HgCl ₂ adduct	—	—	—	—	224-225	345
4'-I	—	—	NO ₂	—	200	199
4'-OH	—	—	—	—	205	221
4'-OH	—	Cl	—	—	239 (dec.); ²²⁵ 240-241; ²⁷⁸ 241; ²¹⁹ 242 ²²¹	219, 221, 225, 278
4'-OH	—	Br	—	—	243	221
4'-OH	—	Cl	—	Cl	251	221
4'-OH	—	Br	—	Cl	241	221
4'-OMe	—	Cl	—	—	143-145; ²²⁴ 144; ²¹⁸ 144-145 ²²⁵	218, 224, 225, 278
4'-OCH ₂ Ph	—	Cl	—	—	142	218
4'-OCOPh	—	Cl	—	—	231	218
4'-OMe	—	Br	—	—	134-135	224
4'-OMe	—	OMe	OMe	—	170.5-173	128
HgCl ₂ adduct	—	—	—	—	203.5-210	128
4'-OAc	—	Cl	—	—	171; ²¹⁹ 172-173 ²²⁵	219, 225
4'-NH ₂	—	—	—	—	113	214, 279
Hydrochloride	—	—	—	—	228	214
4'-NH ₂	—	Cl	—	—	208	215, 279
Hydrochloride	—	—	—	—	245	215
4'-NHAc	—	—	—	—	202	214
4'-NHAc	—	Cl	—	—	222	215

TABLE XIII—continued



Phenyl substituent	4	5	6	7	M.P. (°C)	Ref.
4'-NHCOPh	—	—	—	—	224	214
4'-NHCOPh	—	Cl	—	—	242	215
4'-N=CHPh	—	—	—	—	148–149	214
4'-N=CHPh	—	Cl	—	—	149	215
4'-N=CH—C ₆ H ₄ —NO ₂ (<i>o</i>)	—	—	—	—	155	214
4'-N=CH—C ₆ H ₃ —NO ₂ (2)—Cl(5)	—	Cl	—	—	227	215
4'-NMe ₂	—	Cl	—	—	162–163	222
Methiodide					184	222
Chloroplatinate					> 200	222
2',5'-(OH) ₂	—	—	—	—	200	221
2',5'-(OH) ₂	—	Cl	—	—	254	221
2',5'-(OH) ₂	—	Br	—	—	260	221
2'-OH—5'-Me	—	Cl	—	—	208–209; ²⁷⁸ 210 ²¹⁹	219, 278
2'-OMe—5'-Me	—	Cl	—	—	208–209	278
2'-OAc—5'-Me	—	Cl	—	—	135	219
3'-OMe—4'-OH	—	Cl	—	—	181.5	220 ^b
3'-SO ₂ NH ₂ —4'-Cl	—	—	—	—	244–246	237 ^b

* No data.

^b Structure doubtful.^c Position uncertain.

TABLE XIV
2,1-BENZISOXAZOLIN-3-ONES



R	4	5	6	7	M.P. (°C)	Ref.
—	—	—	—	—	112	138, ^a 146
—	—	—	COOH	—	> 300	145
—	—	—	SO ₃ H	—	<i>b</i>	145
—	Me	—	—	—	119–120	144
—	COOH	—	—	—	190–192; ¹⁴⁵ 191 ¹⁴⁷	145, 147
—	COOMe	—	—	—	110–119 ^c	147
—	COOH	Cl	—	—	178	145
—	COOH	—	COOH	OC ₁₈ H ₃₇	<i>d</i>	145
—	CONH·C ₂₅ H ₄₄ NO ₃ S ^e	—	—	—	212	145
Ac	—	—	—	—	117.5–118.5; ¹⁴⁶ 121 ¹⁴⁹	146, 149
Ac	—	—	—	COOH	190	145
Ac	COOH	—	—	—	212; ¹⁴⁵ 215 ¹⁴⁷	145, 147
Ac	COOMe	—	—	—	119	147
Ac	CONH—C ₁₈ H ₃₇	—	—	—	98–100	145
Ac	COOC ₁₈ H ₃₇	—	—	—	71–72	145

TABLE XIV—continued



R	4	5	6	7	M.P. (°C)	Ref.
COPh	—	—	—	—	153–154	138 ^a , 146, 240
COOEt	COOH	—	—	—	156	145
CONHPh	COOH	—	—	—	190	145
Ts	COOH	—	—	—	206	145
Me	—	—	—	—	49–50 ¹³⁸	138, 146
Me	COOH	—	—	—	163	147
Me	COOMe	—	—	—	66	147
Me	CONH—NH ₂	—	—	—	> 200 ^{c,f}	325
Et	—	—	—	—	<i>g</i>	146
Et	COOH	—	—	—	138	147
CH ₂ OH	—	—	—	—	116–117	240
—CH ₂ —	—	—	—	—	162 ^a	240

^a No data.^b Not isolated from solution.^c Unsharp.^d Waxy solid; no further data.^e C₆H₅·2·NMeC₁₈H₃₇·5·SO₃H.^f As hydrate of hydrochloride.^g Oil, decomposing on distillation.^h Rapid heating.

TABLE XV
ANTHRANIL-1-OXIDES



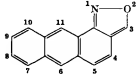
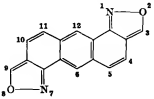
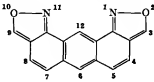
3	4	5	6	7	Decomp. pt. (°C)	Ref.
Ph	—	—	—	—	187–188 ^a	316 ^b
N=N—C ₆ H ₄ —Me(<i>p</i>)	—	—	—	—	143	319 ^c
N=N—C ₆ H ₄ —Cl(<i>p</i>)	—	—	—	—	147	319 ^c
N=N—C ₆ H ₄ —Br(<i>p</i>)	—	—	—	—	144	319 ^c
N=N—C ₆ H ₃ —Cl(2)—Me(4)	—	—	—	—	134	319 ^c
N=N—C ₆ H ₃ —Br(2)—Me(4)	—	—	—	—	139	319 ^c
N=N—C ₆ H ₃ —Br(2)—Me(4)	—	—	NO ₂	—	133	319 ^c
N=N—C ₆ H ₃ —Me(2)—Br(4)	—	—	—	—	151	319 ^c
N=N—C ₆ H ₃ Cl ₂ (2,4)	—	—	—	—	140	319 ^c
N=N—C ₆ H ₃ Br ₂ (2,4)	—	—	—	—	145–146	318, 319
N=N—C ₆ H ₃ —NO ₂ (2)—Br(4)	—	—	—	—	142	319 ^c
N=N—C ₆ H ₂ Cl ₂ (2,6)—Me(4)	—	—	—	—	155	319 ^c
N=N—C ₆ H ₂ Br ₂ (2,6)—Me(4)	—	—	—	—	167	319 ^c
N=N—C ₆ H ₂ Br ₂ (2,6)—Me(4)	—	—	NO ₂	—	142	319 ^c
N=N—C ₆ H ₂ Br ₂ (2,4)—Me(5)	—	—	—	—	126	319 ^c
N=N—C ₆ H ₂ Br ₂ (2,4)—Me(6)	—	—	—	—	145	319 ^c
N=N—C ₆ H ₂ Cl ₃ (2,4,6)	—	—	—	—	163	319 ^c
N=N—C ₆ H ₂ Cl ₃ (3,4,5)	—	—	—	—	151	319 ^c
N=N—C ₆ HBr ₄ (2,3,4,5)	—	—	—	—	155	319 ^c
N=N—C ₆ Cl ₅	—	—	—	—	128	319 ^c
N=N—C ₆ Br ₅	—	—	—	—	157	319 ^c

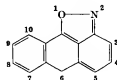
^a M.P.

^b Structure doubtful.

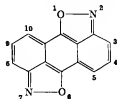
^c Structure based on analogy;³¹⁸ see text.

TABLE XVI
CONDENSED ANTHRANIL SYSTEMS

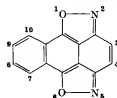
Ring system	Substituents	M.P. (°C)	Ref.
Anthra[1,2- <i>c</i>]isoxazole 	6,11-H ₂ , 6=O, 11=O 6,11-H ₂ , 6=O, 11=O, 3-Me 6,11-H ₂ , 6=O, 11=O, 7-NO ₂ 6,11-H ₂ , 6=O, 11=O, 7,8,9,10-Cl ₄	~ 250 (dec.) ~ 210 <i>a</i> ~ 242 (dec.)	184 184 184 184
Anthra[1,2- <i>c</i> ;5,6- <i>c'</i>]diisoxazole 	6,12-H ₂ , 6=O, 12=O	<i>a</i>	184
Anthra[1,2- <i>c</i> ;7,8- <i>c'</i>]diisoxazole 	6,12-H ₂ , 6=O, 12=O	<i>a</i>	184

6*H*-Anthra[1,9-*cd*]isoxazole

6=O	> 300 ¹⁸⁹	189, 191, 192
6=O, 5-Cl	212	168, 189
6=O, 5-Br	242	189
6=O, 5-NO ₂	244-245	192
6=O, 5-OMe	<i>a</i>	168
6=O, 3-NO ₂ , ^b 5-Cl	187	192
6=O, 7-Py ^c	> 300	192
6=O, 7-Cl	<i>a</i>	168
6=O, 7-N=N-C ₆ H ₄ -NMe ₂ (<i>p</i>)	229	192
6=O, 10-N ₃	<i>a</i>	190
6=O, 10-N=PPh ₃	<i>a</i>	190

Anthra[1,9-*cd*;5,10-*c'd'*]diisoxazole

—	> 300 ¹⁸⁹	168, 189, 190
5-Cl	<i>a</i>	163

Anthra[1,9-*cd*;4,10-*c'd'*]diisoxazole

—	> 300 ¹⁸⁹	189, 190
---	----------------------	----------

^a No data.^b Position uncertain.^c Pyridyl-(4)-.

TABLE XVII

4,5,6,7-Tetrahydroanthranils



3	4	5	6	7	M.P. or B.P. (°C)	Ref.
—	—	—	—	—	35–38/2 mm; ³⁵¹ 87–88/14 mm; ⁹¹ 93/15 mm ⁵⁶	56, 91, 351
—	—	—	C ₆ H ₄ —OMe(<i>p</i>)	Me	161–162	86
—	Me	—	—	—	97/16 mm	56
—	Me	—	—	<i>i</i> -Pr	85–86/1.0–1.4 mm; 76–77/0.45–0.55 mm	84
Ph	—	—	—	—	125–126	326
C ₆ H ₄ —Me(<i>p</i>)	—	—	—	—	95	326
C ₆ H ₄ —Cl(<i>p</i>)	—	—	—	—	137	326
COOH	—	—	—	—	150	94
COCl	—	—	—	—	<i>a</i>	94
COOEt	—	—	—	—	<i>b</i>	94
CONEt ₂	—	—	—	—	49–50	94
NH ₂	—	—	—	—	117–118; ³³⁰ 119; ³³⁴ 130; ³²⁷ 130–132 ³²⁸	327, 328, 330, 334
NH ₂	—	—	—	Me	66–70	327
Hydrochloride	—	—	—	—	78	327
NHAc	—	—	—	—	82–83	327
NHCOPh	—	—	—	Me	95–97	327
NH—Sulf ^c	—	—	—	—	176–179	100, 328, 329
Sodium salt	—	—	—	—	246–248 (dec.)	328, 329
NH—(Sulf-Ac) ^d	—	—	—	—	208–210 (dec.)	328, 329
NAc-Sulf ^e	—	—	—	—	213 (dec.); ³²⁸ 212.5 ¹⁰⁰	100, 328
NCOPh-Sulf ^e	—	—	—	—	222–224	100, 328

N(COEt)-Sulf ^c	—	—	—	—	208	328
N(COPh)—Sulf-COPh ^c	—	—	—	—	198-200	328
NMe-Sulf ^c	—	—	—	—	141-142	328
N(CH ₂ Ph)—Sulf ^c	—	—	—	—	180-182	328
N(CH ₂ CONMe ₂)—Sulf ^c	—	—	—	—	180	328
N(Sulf-Ac ^d) ₂	—	—	—	—	241 (dec.)	328, 329
NH—SO ₂ —C ₆ H ₄ —(N=Naphth ^f)(<i>p</i>)	—	—	—	—	<i>g</i>	333
NH—SO ₂ —C ₆ H ₄ —(N=Naphth ^h)(<i>p</i>)	—	—	—	—	<i>g</i>	333
NH—SO ₂ —C ₆ H ₄ —(N=Naphth ⁱ)(<i>p</i>)	—	—	—	—	<i>g</i>	333
N=CHPh	—	—	—	—	74-76	332
N=CH—C ₆ H ₄ —NO ₂ (<i>p</i>)	—	—	—	—	216-217	327
N=CH—C ₆ H ₄ —NO ₂ (<i>p</i>)	—	—	—	Me	215-216	327
N=CH—C ₆ H ₄ —OMe(<i>p</i>)	—	—	—	—	133-134	332
N=CH—C ₆ H ₄ —NO ₂ (<i>o</i>)	—	—	—	—	127-128	332
NH—CH ₂ —Ph	—	—	—	—	114-115	332
NH—CH ₂ —C ₆ H ₄ —OMe(<i>p</i>)	—	—	—	—	88-90	332
NH—CH ₂ —C ₆ H ₄ —NO ₂ (<i>o</i>)	—	—	—	—	84-85	332
NH—CH ₂ —C ₆ H ₄ —NHMe(<i>p</i>)	—	—	—	—	126-127	332
NMe ₂	—	—	—	—	<i>a</i>	327
Picrate	—	—	—	—	154-155	327

* Oil.

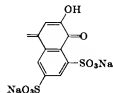
^b Not isolated pure.^c SO₂-C₆H₄-NH₂(*p*).^d SO₂-C₆H₄-NHAc(*p*).^e SO₂-C₆H₄-NHCOPh(*p*).^f No data

TABLE XVIII
OTHER REDUCED ANTHRANILS



Position of extra hydrogen	Substituents	M.P. or <u>B.P.</u> (°C)	Ref.
1,3	3-Ph	116.5	151
1,3	1-Ac, 3,3,6-Me ₃ , 5-OH	193-194	335
1,3	1-Ac, 3,3,6-Me ₃ , 5-OAc	135-136	335
3,5	3,3,6-Me ₃ , 5=O	152-153	335
4,5	4,5-Cl ₂	77	269
4,5	3-Me, 4,5-Cl ₂	99-100; ¹³⁵ 101-101.5 ¹²²	122, 135
4,5	3-C ₁₇ H ₃₅ , 6-OEt	58-60	343
4,5	6,7-Benzo-	114-117/0.3-0.4 mm	84
3,3a,4,5	3,3,6-Me ₃ , 5=O	129-131	335
1,3,3a,4,5,7a	1-Et, 3,3,6-Me ₃ ^a	108-110/15 mm	336
Hydrogen oxalate		136-137	336
Methiodide		158.5-159	336

1,3,3a,4,5,6,7,7a	1-Me ^a	70-72/15 mm	336
Hydrogen oxalate		95-96	336
Methiodide		148-149	336
1,3,3a,4,5,6,7,7a	1- <i>i</i> -Pr, 3-Me	70-80/15 mm	336
Hydrogen oxalate		95-96	336
Picrate		150-157	336
1,3,3a,4,5,6,7,7a	1,3,3,6-Me ₄ ^c	116-118/20 mm; 102-104/16 mm	336
Picrate		168-169	336
Methiodide		198-199	336
1,3,3a,4,5,6,7,7a	1-Et, 3,3,6-Me ₃ ^d	104-105/16 mm	336
Picrate		156-157	336
1,3,3a,4,5,6,7,7a	1- <i>i</i> -Pr, 3,3,6-Me ₃	107-108/12 mm	336
Picrate		144-145	336
1,3,3a,4,5,6,7,7a	1-Ph, 3,3,6-Me ₃ ^e	144-145	336
Picrate		183-184	336
1,3,3a,4,5,6,7,7a	1,7a-Me ₂ ^f	105-106/37 mm	336
Picrate		220 (dec.)	336

^a Predominantly *cis* isomer.^b *cis* isomer.^c 86% *trans-trans* isomer, with others.^d 73-80% *trans-trans* isomer, with 12-14% of a *cis* isomer, and other isomers.^e *Trans-trans* isomer.^f *cis:trans* isomer = 2 : 1.

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Numbers in parentheses are reference numbers and indicate that an author's work is referred to although his name is not cited in the text.

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